FOOD AND DRUG ADMINISTRATION

Clinical Chemistry and Clinical Toxicology Devices Panel

Premarket Notification Submission
For an Over-The-Counter Device
For Measuring Fructosamine
and
Issues Regarding Self-Monitoring
Blood Glucose Systems

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Proceedings By:

CASET Associates, Ltd.

10201 Lee Highway, #160 Fairfax, Virginia 22030 (703) 352-0091

ROSTER:

Chairperson:

Henry Nipper, Ph.D.

<u>Voting Members:</u>

Joann Boughman, Ph.D.
Barbara Goldsmith, Ph.D.
Robert Rej, Ph.D.
Thomas Kurt, M.D.
Beverly Harrington Falls, M.D.

Executive Secretary:

Sharon K. Lappalainen

Temporary Voting Members

Steven Clement, M.D.
James Cooper, M.D.
Arlen Rosenbloom, M.D.
Joanna Zawadzki, M.D.

Industry Representative:

Robert Habig, Ph.D.

Consumer Representative:

Ellen S. Rosenthal, M.S.

TABLE OF CONTENTS

Opening Remarks Introduction	<u>Page</u> 1
Open Public Session	7
Sponsor Presentation: Over-the Counter Device for Measuring Fructosamine LXN Corporation John Burd, Ph.D. William Cefalu, M.D. Ernest Tucker, M.D. John Kennedy Donnell Etzwiler, M.D.	8 13 17 19 26
FDA Presentation Patricia A. Bernhardt	72
Open Committee Discussion	77
Issues Regarding Self-Monitoring Blood Glucose Systems	
FDA Presentation Introduction to Self-Monitoring Blood Glucose Systems Dr. Susan Alpert Steven I. Gutman, M.D.	150 155
Open Public Session Dr. John Ross Ms. Hensen Robert Ratner Diane Lellock Murray Loew, Ph.D. Madelyn Minch	165 177 188 194 201 208
Open Committee Discussion	217
Perspectives on the Current Use of SMBG Devices	
FDA Presentation Medical Device Reporting Sharon F. Dillard, M.S.	241
FDA Presentation Premarket Review Guidance	257

Cornelia B. Rooks, M.A.

Open Committee Discussion

267

PROCEEDINGS

[8:05 a.m.]

Agenda Item: Opening Remarks -- Introduction

MS. LAPPALAINEN: Good morning. I am Sharon Lappalainen, the executive secretary of the Clinical Chemistry Toxicology Devices Panel.

We are here this morning to discuss a premarket notification for an over-the-counter device that measures fructosamine, which is intended to be used as an aid in the management of diabetes.

This submission is under review within the Clinical Chemistry, Toxicology and Hematology Branch in the Division of Clinical Laboratory Devices, affectionately known as DCLD.

I would like to acknowledge our former executive secretary, Ms. Cornelia Rooks. Ms. Rooks now pursues a new position as director of the Division of User Programs and Systems Analysis. She has served with distinction as the executive secretary for the last five years and her service

and dedication are to be commended. She will be sorely missed.

I would also like to personally introduce our new chairperson, Dr. Henry Nipper, seated to my right. Dr. Nipper is an associate professor of pathology at Creighton University in Omaha and he also serves as the dean of admissions to the medical school. He has made many insightful and valuable contributions during his past service to the panel.

Dr. Nipper replaces our former chairperson, Dr. Arthur Carmen(?), whose four year appointment was well-served by both his characteristic style and sense of humor.

Welcome, Dr. Henry Nipper and welcome to our distinguished panel.

At this time, I would like each of the panel members to introduce themselves. Please state your name, affiliation and your current FDA panel advisory membership. I would like to begin with Dr. Arlen Rosenbloom.

DR. ROSENBLOOM: That is it. Arlen Rosenbloom, University of Florida, Gainesville, pediatric endocrinologist and I am a temporary member of the panel.

DR. KURT: I am Tom Kurt from the University of Texas Southwestern Medical Center at Dallas. I am the

founder of the certified regional poison center and a professor of internal medicine. I am a regular member.

DR. ZAWADZKI: Good morning. I am Joanna
Zawadzki. I am an endocrinologist in private practice in
Rockville, Maryland. I am a clinical associate professor of
medicine at Georgetown University Medical Center. And I am
a former member of the Endocrinologic and Metabolic Advisory
Committee.

DR. GUTMAN: I am Steve Gutman. I am the director of the Division of Clinical Lab Devices.

DR. COOPER: I am Jim Cooper. I am a geriatrician and I am a senior medical adviser in the Agency for Health Care Policy Research, another Public Health Service agency, and I am also on the faculty of the Uniformed -- what is the name of our university -- University of Health Sciences of the Uniformed Services.

DR. GOLDSMITH: Good morning. I am Barbara

Goldsmith. I am the associate director of lab medicine at

St. Christopher's Hospital for Children in Philadelphia and

also the director of clinical chemistry there. I am also

the associate professor in the Department of Pathology and

Laboratory Medicine at MCP Hahnemann School of Medicine,

which is part of Allegheny University of the Health

Sciences.

DR. REJ: I am Robert Rej. I am director of clinical chemistry and hematology at the New York State Department of Health in Albany and associate professor of biomedical sciences in the School of Public Health at the State University in Albany.

DR. BOUGHMAN: Joann Boughman, University of Maryland. I am a geneticist by training, currently vice president for academic affairs and dean of the graduate school.

DR. REJ: I am a voting member of the panel.

DR. BOUGHMAN: I, too, am a voting member of the panel.

DR. CLEMENT: Steve Clement, an adult endocrinologist, presently director of the Georgetown Diabetes Center here in Washington, D.C. I am a voting member -- I am sorry -- a temporary voting member of the advisory panel.

DR. HARRINGTON FALLS: Beverly Harrington Falls,

Cornerstone Health Care in High Point, North Carolina. I am
an OB-GYN and I am a temporary voting member of the panel.

MS. ROSENTHAL: I am Ellen Rosenthal. My background is actually in engineering and I am the consumer

rep to this panel.

DR. HABIG: My name is Bob Habig. I am the other non-voting member of this panel. I am the industry representative and contrary to what it says on the document, I work at Becton(?) Dickinson and Company. I used to work at Bayer Diagnostics.

MS. LAPPALAINEN: I would like to read for the record a conflict of interest statement for the Clinical Chemistry and Clinical Toxicology Devices Panel meeting for March 20th and 21st, 1997.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interest.

However, the Agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the

government.

We would like to note for the record that none of the participants reported any involvement related to the fructosamine issue. A waiver has been granted to Ms. Ellen Rosenthal for her financial interest in a self-monitoring glucose SMBG firm that could potentially be affected by the committee's deliberations.

The waiver permits this individual to participate in all matters before the panel. Copies of this waiver may be obtained from the Agency's Freedom of Information office, Room 12A-25 of the Parklawn Building.

We would like to note for the record that the Agency took into consideration other matters regarding Drs. Barbara Goldsmith and Henry Nipper. The financial interests reported by these individuals are not related to the SMBG matter before the panel. Therefore, the Agency has determined that they may participate fully in the panel's deliberations.

We also note that Dr. Arlen Rosenbloom reported test strip studies with SMBG firms. However, since the studies ended more than ten years ago, the Agency determined that he may participate in the panel's deliberations.

In the event that the discussions involve any

other products or firms not already on the agenda for which the FDA participant has a financial interest, the participants should excuse themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm, whose products they may wish to comment upon.

Additionally, I would like to state for the meeting today and tomorrow, Ms. Ellen Rosenthal will serve as consumer representative and Dr. Robert Habig will serve as the industry representative.

The following are our current members on the panel: Dr. Joann Boughman, Dr. Barbara Goldsmith, Dr. Robert Rej, Dr. Thomas Kurt and Dr. Beverly Harrington Falls.

Additionally, I will read the following consultants to the panel: Dr. Steven Clement, Dr. James Cooper and Dr. Arlen Rosenbloom.

Now, I would like to turn the meeting over to Dr. Nipper.

DR. NIPPER: Thank you very much. I would like to

add my appreciation to the FDA staff and predecessors who have tried to train me in what I am supposed to do today.

Agenda Item: Open Public Session

We are about to move to an open public session and in this open public session, public attendees who contacted the executive secretary prior to the meeting will address the panel and present information relevant to the agenda.

Speakers are asked to state whether or not they have any financial involvement with manufacturers of any products being discussed or with their competitors. So, I will declare that the open public session is now open.

Are there people who would like to present to the panel?

Hearing no people who have come forward to present, I think we will now move to the sponsor presentation. We have a full day today. So, we will take advantage of a few extra minutes, but we would like to keep on the clock as much as possible.

So, the representatives of the LXN Corporation, please come forward.

Agenda Item: Sponsor Presentation: Over-The-Counter Device for Measuring Fructosamine

DR. BURD: Shall we begin?

DR. NIPPER: The floor is yours.

DR. BURD: Good morning, everyone. My name is John Burd and I am president of LXN Corporation. I guess that establishes the financial considerations that we are supposed to announce.

As I said, I am president of LXN Corporation. We are a San Diego company that is dedicated to the development of new self-testing products to help people with diabetes. I have a Ph.D. in biochemistry from the University of Wisconsin and I have spent the last 25 years developing new medical testing products both at Miles Laboratories and at Quidel(?), prior to becoming a co-founder of LXN Corporation.

I am very pleased to be able to present to the FDA panel our 510(k) submission on the LXN fructosamine test, which we believe to be safe and effective and providing great benefits to persons with diabetes without any significant risk.

At the end of the day, I will be asking you, the panel, to recommend to the FDA that our OTC fructosamine test be given 510(k) clearance.

Since our time is limited, I would ask that you please hold the questions until after we finish the

presentation.

Could I have the next slide, please?

Well, this slide summarizes what we believe are the key benefits of the OTC fructosamine test. The reason we developed this test was to fulfill an important need among need among people with diabetes. We wanted to provide them with a fast, safe and convenient way to monitor their overall glucose control.

Glycated protein tests are recognized as the gold standard for monitoring glucose control and fructosamine is a glycated protein test with special applications for diabetes self-management. We chose to work with the fructosamine assay because it has been proven to be a very sensitive indicator of glucose control. It measures the true average of continuous glucose levels over a very tight recent time frame, two to three weeks, a time frame that is especially useful for measuring recent visemic(?) control and we chose to develop the self-test format to make it practical.

Laboratory testing of glycated protein is simply too inconvenient and too costly to perform frequently enough to allow truly effective monitoring. Well, let me tell you a couple of things that the OTC fructosamine test will not

do. First of all, the OTC fructosamine test will not replace blood glucose testing or glycated hemoglobin testing.

OTC fructosamine has been developed to compliment these tests for enhanced diabetes management. Secondly, the OTC fructosamine test will not distance the diabetic patient from the health care professional. It will bring patients closer to their care givers. All of our product labeling directs patients to work with physicians for guidance about how to use the fructosamine test results.

Like blood glucose test results, our OTC labeling does not give specific values, but directs patients to incorporate fructosamine test results into their management program with the assistance of the health care professional. Fundamentally, the great value of the fructosamine self-test is that allows persons with diabetes to know how well their management program is working.

If the fructosamine results indicate poor glucose control, that is, the results are outside of the individualized target ranges for that patient, then that patient can work with their health care professional to improve their diabetes management program. If the fructosamine test indicates good glycemic control, patients

and their health care professionals will know that the diabetes management program for that patient is working.

As you will learn more today, these many benefits far outweigh the potential risks of OTC fructosamine, which we think to be few and of minor consequence.

Could I have the next slide, please?

In order to show that this product is substantially equivalent to predicate devices, LXN followed the FDA's 1996 blood glucose guidance document and we conducted the various studies shown on this slide. These studies were precision studies, interference studies, linearity studies, hematocrit studies and accuracy studies.

LXN's 510(k) submission for OTC fructosamine cites several predicate devices, each of which has already received 510(k) clearance from the FDA. These devices include both fructosamine laboratory tests, as well as OTC predicate blood glucose self-tests.

I would like to summarize first the predicate fructosamine lab tests.

Next slide, please.

This slide shows the four OTC predicate fructosamine tests made by LXN, Roche, Cigma and Berringer(?) Manheim Corporation. The similarities of these

four tests to the LXN OTC fructosamine test are that they all measure fructosamine. They all use basically the same chemistry. They all use a color measuring spectrometer and they are all cleared by the FDA for laboratory use.

Next slide, please.

This is slide summarizes the predicate OTC devices for self-testing. All of these tests measure blood glucose and they are manufactured by LXN Corporation, LifeScan and Berringer Manheim. The similarities of these four devices to the LXN OTC fructosamine test are that they are all labeled for OTC use. They all use a calorimetric reflectance photometry. They all measure an anilide in capillary whole blood. They are all rapid tests and they are all for home use by persons with diabetes.

The next slide, please, shows the regulatory history for the LXN fructosamine test. As you can see, LXN's fructosamine test has already been shown to be substantially equivalent to other laboratory fructosamine tests. Our test was cleared for laboratory use exactly one year ago today. Today, of course, we are seeking OTC clearance for the LXN fructosamine test.

Next slide, please.

To support this change in the intended use of the

LXN fructosamine test from laboratory to OTC, we have undertaken four key initiatives, which are the same initiatives that would be used to evaluate a new home blood glucose test. These four initiatives were clinical studies, precision studies, human factor studies and OTC labeling according to FDA guidelines.

In our presentation today, we will share the results of each of these initiatives with the panel.

Next slide, please.

To ensure proper device labeling for the OTC fructosamine test, we followed two FDA guidance documents, one NCCLS guidance document and we relied upon our reviewers' comments, which we obtained from the FDA during the earlier process of our obtaining OTC clearance for the LXN glucose test.

The next slide, please.

This slide summarizes the sample size and the results of LXN's human factor studies for our OTC fructosamine test. In our human factor studies, we surveyed test participants after they performed the LXN fructosamine test and asked them if they found the system easy to use. As you can see, over 95 percent said "yes." Again, these human factor studies were performed according to the FDA's

1996 DCLD guidance documents.

To help panel members more fully understand the risk/benefit analysis of LXN's fructosamine test for OTC use, I have invited experts in diabetes and clinical chemistry to make short presentations today. I would like to begin those presentations with Dr. William Cefalu of the Bowman Gray Medical School at Wake Forest University.

DR. NIPPER: Doctor, before you start, let's -- if you are going to use slides, it may be easier for you to use that clicker, but I am not sure it is working. It may be just easier to call for the next slide then. That would be fine.

DR. CEFALU: Good morning. I am Dr. Cefalu. I am an associate professor of medicine at the Bowman Gray School of Medicine at Wake Forest University. I am also director of the Diabetes Conference of Care and Research Program there. I am also here to tell you that I have no financial interest in the device discussed this morning.

I am here today to share with the panel my insights into the clinical applications of fructosamine testing in the management of diabetes. I am convinced from my own research and from first hand experience with this device that fructosamine testing in general and the LXN

fructosamine in particular are reliable markers of glucose control in patients with diabetes.

During the last ten years, I have published over nine articles on this particular assay that talk about fructosamine use in diabetic patients, in Type I patients, Type II, for screening geriatric patients, et cetera. I have given literally dozens of presentations on this topic.

Today, I would like to begin by sharing with you a little bit about the history of fructosamine. Fructosamine has been steadily increasing in use in diabetes management over the past decade. Currently, there are four major manufacturers for test kits for measuring fructosamine in clinical laboratories. The fact that fructosamine measures overall glycemic control over the previous two or three weeks offers a certain advantage over the other major glycated protein tests, that being glycated hemoglobin, which measures glucose control over the previous two to three months.

Fructosamine is the more sensitive test to recent changes in glucose control.

Can I have the next slide, please?

In 1990, the importance of diabetes management to knowing the results of glycated protein tests was

demonstrated in a study by Larson, who showed that when doctors and patients know their glycated protein levels, they were able to achieve better glucose control. We are all familiar, I think, with the results of the DCCT or the diabetes control and complications trial that suggest that when glycated protein levels were measured and followed, that these levels correlated to reduce complications in the diabetic patient by as much as 70 percent.

The LXN fructosamine test is important because of its self-test format, which gives persons with diabetes a first ever practical means for frequent monitoring of their recent glucose control. It is noteworthy that the chemistry used in the LXN fructosamine test is the same as that used in extensively validated laboratory fructosamine test methods.

Can I have the next slide, please?

This slide shows the chemistry of the fructosamine reaction. Glucose in the bloodstream reacts with the amino groups of all proteins, for example, albumin and hemoglobin to form what is called a shift base. This shift base then rearranges to a stable compound called a ketoamine, which we refer to as the fructosamine. In the fructosamine test, the sample is made alkaline to generate an anolamine(?), which

is a good reducing agent. This anolamine reduces a catchazolid(?) in salt to generate a culled reaction product, which is then measured in a spectrophotometer.

The rate of color production is directly related to the amount of fructosamine in the sample. I have actually shown in my own research that the lab fructosamine test is clinically comparable to the Roche Laboratory fructosamine test. And I would be more than happy to share with you the results of my result research.

So, what should we conclude from this? Simply that the test chemistry of the LXN over-the-counter fructosamine test is equal to that of the commercially available fructosamine tests.

Now, I would like to allow Dr. Tucker to make a few comments.

DR. TUCKER: Good morning. I am Dr. Ernest

Tucker. I am the head of pathology at Scripps Clinic in La

Jolla. I have been in pathology for almost 40 years and

have been director of clinical laboratories in a number of

major medical centers and am quite familiar with the

fructosamine test.

I am here today because I am a consultant for LXN.

I am on their scientific advisory board and I do have this

disclosure that I have a financial relationship with LXN Corporation.

My first slide is a history of the sites that were used in the studies of the LXN test for the OTC fructosamine. We had four sites and these sites, the individual patient numbers studied at each site are indicated. The dates of the study are shown. The studies at each of these sites followed the FDA guidance documents and FDA reviewer guidelines.

Two studies were performed. The first study was in June of 1996. It was a performance of the LXN test with 51 patients in San Diego and 50 patients in La Mesa, California -- 51 patients in Santa Fe. I am sorry.

The Food and Drug requested that none of the patients in these studies receive any training on the LXN test prior to running the test and for this, the patients were brought in and each patient performed a finger prick and by the same method a technician then pricked another finger in the patient and obtained a sample similar to that obtained by the patient.

These were compared together. The second test strip that was obtained by the technician served as the comparison. The comparison was then made to the LXN device

that had been cleared previously by the FDA for us in 1996.

And, in addition, there was a venepuncture sample drawn from the subject and this was tested in yet another system, the Roche Rotag(?) fructosamine system.

Based on the reviews that I have done of the data and the comparisons of the performance, I believe that the LXN test in these OTC areas gives essentially the same results as the test to which they are compared.

You will hear more about this in the presentation from John Kennedy, who is a LXN consultant, a biostatistician, in the next presentation. But before Mr. Kennedy presents that information, I would like to discuss just briefly some of the precision studies that LXN performed in their 510(k) submission.

Next slide.

This gives a brief view of the professional technician's performance of the assay versus the participant performance of the assay. As you can see, the LXN test strip gave coefficients of variation ranging from 2.4 percent to 5.9 percent. This is shown along the bottom portion of the slide.

The study participants who were the individual participants are shown along the bottom of the slide and the

professional participants along the top and you will also notice that their CVs ranged in the range from 2.6 to 6.6 percent, from the higher to lower values, a comparable range to that found by the professionals.

Thus, from my review of the LXN 510(k) submission, looking at the data and the summaries of the data that I have seen in terms of graphic and tabular form, I feel that from the point of view of the clinical chemistry performance, the LXN fructosamine test in the hands of a lay user will perform and is as safe and effective as any comparable devices that now are approved for laboratory use.

I have reviewed these conclusions with Mr. John Kennedy, who is a biostatistician consultant for LXN and John Kennedy is here today to further discuss the details of the statistical analysis of these studies.

Thank you.

MR. KENNEDY: I am going to be using overhead slides, so if I could have the slide projector off, and if there is any way to turn off the overhead lights at the front of the room, could we try to do that?

Good morning, ladies and gentlemen. As Dr. Tucker mentioned, I will be presenting a brief summary of the primary performance evaluation data that was collected

during the clinical trials of this product. Since our time is limited, I am going to present a series of method comparison scatter plots. These scatter plots are drawn on equally scaled axes and display the singlicate method comparison results of the LXN fructosamine assay.

This is intended for over-the-counter use by lay persons with diabetes. The comparisons will be to two other test results. The first, the predicate, LXN fructosamine test, cleared by the FDA for laboratory use. That was done on a separate finger stick performed by a technician.

The second set of comparisons with the results of the assay of venepuncture blood on the predicate Roche Rotag laboratory analyzer and test system. All this data is presented in support of the substantial equivalence of this assay to laboratory testing for this anilide when the OTC assay is employed in the hands of first time users.

Further, the data seem to support that the users can produce clinically useful test results with only reference to the package insert and instructions.

Finally, this technology provides an important adjunct in helping people with diabetes work with their primary care physicians to manage their disease.

I am going to show you these method comparison

results separately by clinical trial site first and then pooled across the study sites for all of the approximately 300 patents that were tested during this clinical study.

The slide you see up there in front of you, the first slide, is the method comparison data of the test device performed by the untrained participant compared to the results obtained on the same device by a medical technologist, using a separate finger stick done right after the user assay.

The data you see here is from the San Diego sites, combined over time periods that were studied in San Diego.

Underneath the plot are the estimated biases that result from the fitted linear lee(?) squares regression line.

These exhibited biases are small compared to the reported results, as evidenced by the percent bias column, which is outlined in the box.

The pattern that you see here, going from a positive bias at the lowest end to a slight negative bias at the upper end is typical of all of the data here and partially results from the fact that this linear regression is done with error in the x variable.

Since this method of analyzing method comparison data is common, however, and is conservative, this is how

the data is presented to you in the submission before you.

As suggested in the NCCLS EP9 guideline for method comparisons and bias estimation using patient samples, examination of the estimated bias is the proper way to observe the joint effects of slope and intercept in a method comparison experiment.

No outliers have been removed from this data or any of the data presented this morning. For those who are interested, the bias that you see there measures the distance of that regression line from the 1-1 line of identity and represents what is anticipated as the expected difference, expected average difference, between the two methods being compared. It is done and estimated separately at different concentrations as no single value is properly representative of the behavior of the device over the entire range.

The percent biases represented at this study site range between plus 6 percent to minus 8 percent, with an n of 194 patients.

Can I have the next overhead, please?

This is the data from the Santa Fe site. There are 49 patients at this site and the estimated biases are listed at the bottom. Again, the pattern is pretty

consistent and remains so throughout the sites.

The magnitudes are small compared to the measured actual fructosamine levels and I wanted to mention that when you examine this data and make your assessments as to the substantial equivalence of the two methods, don't be misled by the magnitudes of the slopes and the intercepts.

The proper way to assess the effect of slope and intercept is to examine the estimated bias throughout the range. At this site, there was less data and a narrower range of the data collected. The biases here were slightly larger than those in San Diego.

Can I have the next slide, please?

This is the data which compares the LXN fructosamine over-the-counter assay to the professional assay at the La Mesa study site. The biases here were essentially the same as those from the other two sites.

Can I have the next one?

This is the data pooled across all study sites, all time period study. The n is 291 and the biases range from 7 percent to 9 percent on the negative side.

That is the summary of the comparison of the overthe-counter assay to the professional assay.

Can I have the next overhead, please?

I am going to run now through the comparisons of the over-the-counter results -- the same over-the-counter results, compared to the venepuncture Roche assay. The biases exhibited by the data are fairly small again compared to the levels of fructosamine being measured. These values are slightly higher at the edges of the range because of the fact that we know less about bias at the edges of the data range.

Can I have the next slide, please?

The data from Santa Fe for over-the-counter results against Roche. The data at this site was, again, available only in a relatively narrow range and the effects of the error index are magnified at the outer edges, but we believe are still acceptable.

The next slide, please.

This the data from La Mesa. One aspect, this is the first study site involved in the study and the scatter is somewhat higher at this site and upon investigation, it was discovered that the venepuncture samples used for the Roche assay at this site were stored for eight hours and then run as a batch at the end of the day. This resulted in more error in the Roche assay and a higher scatter in the data, with a concomitant higher effect of the error in x

variable on the regressions.

This degree of scatter was not observed at the other study sites, which did not do the same sort of storage of the venepuncture blood.

Next slide, please.

Pooling the data from all three sites again for this comparison, La Mesa data has been included here. Although the poolability of that data could be argued, we feel it is conservative to include it in the overall assessment. The estimated biases here run from 14 percent down to the very edge, the lower edge of the data at 14 and up to a negative 11 percent at the high end.

It should be noted that throughout these patterns, the smallest biases occur near the medical decision level of nominally 300 to 400. That is where the smallest biases are and that is where you want the smallest biases to be.

Can I have the next slide here?

In order to contrast the comparison of the OTC test to Roche to the results of the professional from Roche, the same set of slides were done with the comparison of the professional test to Roche. This is the data from San Diego. Again, biases on the same order and with the same pattern.

Can I have the next slide, please?

And Santa Fe, again, with smaller amount of data in a narrower range.

Next slide, please, is La Mesa, professional use versus Roche. Okay. The increased scatter here, again, due to the eight hour storage of the Roche data is apparent.

And, finally, the final overhead, please, or the final method comparison. This is the pooled data, which shows the relationship of the professional results to Roche. We have taken the conservative approach of exhibiting the bias at 200. I don't think anyone is clinically particularly interested in a bias of 200, but we have included it here down at the very lowest end of the data just for completeness because we go all the way up to the upper end of the data at 700.

All of these relative biases are quite small compared to the level of fructosamine being level.

That is the end of the presentation of the method comparison results.

Can I have the final overhead, just to reiterate what Dr. Tucker already presented. These are the within individual CVs, which resulted on a series of ten diabetics, who were brought in and told to assay this data five times.

The CVs that were achieved ranged between 2.6 and 6.6 percent.

In conclusion, I believe that the data support the ability of the test to produce reliable results that correlate to the laboratory assays of fructosamine even from this data, which is initial results from first time, uninstructed lay users, who had access only to the patient package insert.

Now, the concluding comments of the morning will be given by Dr. Donnell Etzwiler.

DR. ETZWILER: Good morning. And thank you. I am Don Etzwiler and I am founder and now president-emeritus of the International Diabetes in Minneapolis.

I do have a limited number of options in response to serving on the advisory panel for this company. I have just recently retired after 40 years of practice in Minneapolis and many of you know me as a long term advocate or spokesperson for the advancement of diabetes care. I am particularly interested in the comprehensive systems approach to chronic care management and that includes combining scientific knowledge, patient responsibility and cost effectiveness.

Today, I am here to speak on the risk/benefit of

the LXN OTC fructosamine test from the point of view of a practicing physician.

The achievement of good diabetes care, as we all know, is largely data driven. We also know from the DCCT studies and from recommendations of the American Diabetes Association that all persons with diabetes should have regular glycated hemoglobin tests. Fructosamine testing, as we see it, is another important and complementary data point for clinicians.

The development of the fructosamine self-test makes it practical for the first time to foster frequent and regular tests for fructosamine. The self-test is easy. It is convenient. It is informed and provides information from frequent glycocyamine self-testing monitoring.

I believe it will round out the data gap that we have as we work with patients. Obviously, blood glucose monitoring was a tremendous step forward. Hemoglobin AlC, we saw its benefits certainly in the DCCT. The time differentiation between these in terms of glucose, giving you spot tests during the day and just a limited insight, and then, of course, the hemoglobin AlC giving you a mean factor over about two to three months and now an intermediate data point seems to be highly advantageous.

Could I have the next slide?

Late last year we had the opportunity to supervise an evaluation of LXN fructosamine test system at the International Diabetes Center and at this we certainly asked it to be evaluated by patients, by doctors and nurse educators and including a survey among 142 doctors, both in internal medicine, pediatrics and family practice.

More on that data would be available upon request.

The purpose of this evaluation was to determine the utility of OTC fructosamine testing, as perceived by health care professionals and the patients in which these were both evaluated, the product among groups who had experience and inexperience with its use.

Our study included a hands on evaluation of the product at the IDC, as well as a survey response in which we had 90 physicians respond. From this study, we found both patients and their health care professionals felt that an OTC fructosamine test would likely provide important knowledge, enhanced diabetes management and actually foster a sense of personal empowerment among patients.

We also collected physician opinion that suggested there would be little likelihood of harm from potential misuse of the fructosamine self-test in the hands of

patients, using this system in their homes. We do have data that we would be happy to share with you at a later time.

In conclusion, from the viewpoint of a practicing clinician, I am very comfortable with the risk/benefit of the LXN OTC fructosamine test. The potential benefits are great. The potential risks are very small. And I regard the availability of such an OTC fructosamine test as an important enhancement in diabetes management.

I would be happy to answer any of the questions that you have now or later.

Thank you.

DR. BURD: Thank you very much.

That concludes our presentation.

DR. NIPPER: Thank you.

Since we saved a little time in the open public session, I wonder if it would be possible at this time for our panel to ask any questions that have resulted from your presentation.

Dr. Rosenbloom, maybe we will start with you and then we will move around the table and end up with Dr. Habig.

We have about -- we have got a few minutes. So, we can ask questions.

DR. ROSENBLOOM: Should these questions be directed just at the presentation or at the material that was distributed as well?

MS. LAPPALAINEN: Both. You can use the material that you have in front of you or if you have any questions concerning the presentation.

DR. ROSENBLOOM: I have several questions and the first is -- the first question I have has to do with the whether or not this system would replace hemoglobin A1C. I am not sure that in practice one would need both of these. And from a cost benefit, the hemoglobin A1C runs upwards of 65, 85 dollars now in laboratories. Many of us are doing it in our own clinics and not recouping from third parties adequate funding to continue doing it, despite the fact that we need that information at the time we are seeing the patient.

I wonder if it really will be necessary to continue both of these systems. My colleagues and I have thought not, that with a good fructosamine assay that there would be situations, an occasional situation, where you would want both. You would want the hemoglobin A1C to be available, but that for month-to-month management that the hemoglobin A1C might be rendered redundant.

DR. CEFALU: I would like to answer that question.

My name is Dr. Cefalu. And actually we have addressed that question. The question, again, I will state, are they redundant assays? Do they share the same information?

We have actually looked at that clinically. The glycated hemoglobin, an overall measure, is not as sensitive and we have published, in fact, in our clinical chemistry article, where we looked at the correlation between the two. One would argue that in a patient in which is stable and has not achieved recent intervention, that the correlation with the two would be quite high.

However, once you begin to treat the patient and to aggressively treat the patient, that the fructosamine is much more sensitive to those changes. In fact, in our clinical chemistry study, where we achieved aggressive intervention and monitored both average glucose control, fasting sugar and fructosamine, the glycated hemoglobin lagged behind considerably the information achieved from the fructosamine and multiple finger sticks throughout the day.

In fact, by the end of this eight week study, the correlation with the two was poor because the hemoglobin A1C was still dropping, although the fructosamine was completely

normalized.

So, my argument would be in a situation like that that they demonstrate two types of information. One is for more recent changes and one over the previous two to three months. Now, again, the argument would be that if you have a stable patient that has been stable for months, that one or the other may be indicated. However, to pick up the short term changes in management, this is clearly the advantage of the fructosamine and we have that documented in a number of articles.

DR. BURD: My name is John Burd.

As pointed out in Dr. Etzwiler's presentation, we really are not as a company making a statement about not using blood glucose testing or not using hemoglobin A1C testing. We see the fructosamine test, especially as a self-test, very complementary to the tests that are currently being done today so that patients still will utilize their blood glucose testing and for the physician that is seeing the patient, only occasionally, every three months, then the glycated hemoglobin test may still provide them very useful information.

It may also be worth noting that glycated hemoglobin testing, although it is clearly established as

the gold standard, its use is still lagging in the general diabetic management program.

DR. CEFALU: I would like to make one other statement. Again, I think we need them both. The fructosamine -- trends in the fructosamine will predict the later glycated hemoglobin test. So, I don't think it is going to replace. I think it is just a more sensitive test.

DR. ROSENBLOOM: I am not sure I have heard anything that conflicts with the notion that, except for an occasional situation where one would want to look at recent changes and make decisions on that relative to long term, that the number of hemoglobin AlC determinations would be --wouldn't be markedly reduced by having this data available. But I think that those comparisons need to be made. I don't think that both of them are necessary.

DR. ETZWILER: Don Etzwiler.

Certainly changes in therapy, you would like to evaluate at intervals and, as a matter of fact, in insulindependent young diabetics, I usually like to look at the last two weeks of data. The reason for that is -- well, an example would be living in Minnesota, young children, who are gathering data by blood glucose monitoring, let's say, between March and April and they come in and see you in June

and if it is a download even of glucose monitoring at that point, you are dealing with sort of pooling of data and hemoglobin AlC reflects over a three month period.

It is dark fairly long in Minnesota and it is fairly cold. So, if I use that kind of back data over three months now to change my dosages in June when the sun is going to be up there until 10 o'clock at night and that they are now out of school and very active, that gives me a very limited -- I am pooling too much data and what I really want to know what has happened recently to them.

So, very frequently, although we are presented with all of this data by glucose monitoring, I sort of look at to say are they doing it, are they changing, but the data that I make decisions on are the last two weeks usually. I like a two week period for evaluating data because it gives me two Mondays and two Saturdays and two Sundays and the basic thing in adjusting insulin dosage are really looking for patterns. These days and activities vary. So, if I make an alteration, it is very helpful to have a playback in two to three weeks.

Now, within the DCCT, even though hemoglobin A1C reflections over a two or three month period, we obtain them every month and we use that data every month, not only to

manage patients, but all of the sites were surveyed and it was sort of a nudging factor. If your AlCs were moving up a little, even though they were at monthly intervals, action was taken. So, it would have been very helpful when you have a patient whom you are changing medications or there are drastic changes in activities and so forth, to have a two week check on that.

We currently try to do that by phone call. The problems with phone calls are if you are dropping, you know, two weeks of data, blood glucose, you are dropping about 56 -- 40 to 50, perhaps, tests during that period of time. It takes a long time to gather. We found in the DCCT when we were doing weekly assessments of these patients, it took 15 to 20 minutes because you don't just say, gee, I had a 30 -- a patient doesn't just say I had a 35. You say 35. You know, what caused that.

So, when we looked at the costs of monitoring that we did in the DCCT, we are talking about major costs. You are talking about 15 to 20 minutes of professional time.

Now, most physicians don't make those kind of call me in a couple weeks mainly because it is a tremendous time consumption.

And the other factor is consequently it is costly

and, third of all, you are liable. So, if you had sort of a fructosamine that might give you a mean over that period, it would be much more rapidly transmitted and probably used very frequently.

DR. ROSENBLOOM: I should clarify the situation where I would see both sets of data or both kinds of data. Of value would be the individual who has a ten day illness or a five day illness, can have quite a remarkable increase in hemoglobin A1C and then you see them a month later. Hemoglobin A1C, which is more responsive to sin and to repentance, as Bob Tattersall once said, may still be elevated; whereas, your fructosamine may be low and that might have some educational value or whatever.

But, in general, I think what I am hearing is that fructosamine offers a better way of monitoring diabetes clinically than does hemoglobin A1C. Now, I don't use fructosamine. So, this is a very unbiased comment.

DR. CEFALU: There are actually some clinical states in which fructosamine may be more advantageous and one of those is pregnancy, where you get a hemoglobin A1C, you do not want a glucose control for the two months previously. You want it for the previous two months. So, I just wanted to add that.

DR. ROSENBLOOM: Well, that is -- we can drop that issue for the moment, but it does relate to my other question. The packaging of the strips -- I was very concerned about the stability of the strips, having done some studies on other kinds of strip stability -- is six strips per bottle with a shelf life after opening of four weeks. That means that the person would have to test every -- that is 28 days. Six into 28, every five days to use up the strips. That does not seem to be consistent with the recommendation of the frequency of testing, which would be every couple of weeks.

I would like some explanation of the rationale between this.

DR. BURD: Well, the final packaging for the product is actually still being considered and the stability testing of the product relative to open shelf-life stability and so on is still taken into account. So, the final packaging, if six tests per strips are the final packaging decision, we will be sure that the package has at least a three month open bottle shelf life.

DR. ROSENBLOOM: Okay.

In the response to Question 10 in the packet, there is a great deal of blood glucose monitoring data, more

than I get in a typical clinical from the same number of patients. I wondered -- either I missed it or I didn't quite understand your response to the question -- was any attempt made to correlate that blood glucose monitoring data with the fructosamine assay? For example, in the early studies of hemoglobin A1C, it was remarkable how good the correlation was with a single blood glucose, leading some people to say, well, that is very interesting but why not just do a blood glucose.

Of course, correlation is a lot different than information you get from an individual patient.

DR. BURD: The way these studies were performed, again, at LXN, we advertised in the newspaper for volunteers to come in for the study and basically we asked the patients to bring in their diaries. And as I am sure you know, the correlation of glucose test results to fructosamine is going to be very dependent upon the number of times the patient happens to test and the time of day at which they test.

So, we actually did not rigorously go through and compare that individual blood glucose test data to the fructosamine data. However, there are literature studies that have been done --

DR. ROSENBLOOM: There are statistical methods for

correcting for the frequency of testing and so on.

In any of your studies, DR. Cefalu, do you have that data?

DR. CEFALU: Yes, we do. In fact, we have -- to alleviate the problem of multiple devices in patients, what we have done is studies where we have used one device and asked the patient to check their blood sugars at specified times throughout the day. These times were before meals and at bedtime. And we did these studies for six to eight weeks at a time and we actually did weekly fructosamines, weekly average blood glucoses and then looked at the correlations weekly.

What we found was that -- and this is published data -- that the fructosamine has its best correlation with the one week data and also by two weeks. By the time you get out to six weeks, the correlation in our study was like .49; whereas, the hemoglobin A1C had a poor correlation the first week and increased, so they are actually inverse again, supporting our point that you are really measuring two time frames for glucose control.

But I will be happy to share that data with you. We have done those correlation studies with one meter, with specified time points and the fructosamine did correlate.

The laboratory testing did correlate quite well with the home glucose test in this system.

DR. ROSENBLOOM: I just have one more question of what has come up in the discussion.

it is stated that the device is not recommended for use in pregnancy, if I recall. And, yet, pregnancy would seem to be one of the best indications for one to two week evaluation of blood glucose average.

Could you expand on that a bit?

DR. BURD: Yes, I can.

Basically, that labeling comes from the predicate laboratory fructosamine test devices, where the FDA has requested because there is some controversy about the utility of the fructosamine test. There is data that indicates it is useful and data that indicates that it is not useful. Since we have not done studies on its use in pregnancy, that is the reason that that bit of labeling is included.

DR. ROSENBLOOM: I will relinquish the questions to Dr. Kurt.

DR. NIPPER: Thank you, Dr. Rosenbloom.

Dr. Kurt.

And when the respondent replies, it helps the

person on who is doing the taping to just state your name.

I know that seems redundant, but help us out there, please.

DR. KURT: I am Dr. Tom Kurt from Dallas.

I have two principal questions. The first has to do with the test strips themselves. The pricing of such a testing device is often such that the device is priced low and you are selling actually the strips. Consequently, patients have been known to cut test strips in two to save money.

Have you looked at the kinds of results that you might receive under these less than ideal circumstances when patients are cutting test strips in two to save money?

DR. BURD: We have actually built that into the device. It would be virtually impossible. It is a molded plastic test strip part that cannot be disassembled. It would not function if it tried to be -- something like that tried to be done.

I am sorry. This is John Burd speaking. So, the fructosamine test cannot be adulterated in that way.

DR. KURT: My second question has to do with the testing, which was described as ideal at a maximum temperature of 81 degrees Fahrenheit. When you are in more tropical circumstances, such as San Diego or living in

Hawaii, where sometimes the ambient conditions are such that there is not air conditioning, but you have an ambient flow through a building, rather than air conditioning. The temperature might be 85, 87 degrees. Have you looked into the actual ambient test circumstances and the results that you get under those ambient conditions?

DR. BURD: John Burd speaking.

Yes. Basically, the meter for the fructosamine test has temperature monitoring as part of the system, so that if the ambient temperature is outside of the acceptable range, it would not -- it would give an interim message, which would say that the test is outside of that range.

The other thing that may be relevant to that is that the fructosamine test is an occasional test, so that it is not something that you -- it may be dissimilar to the glucose test, where you would want to carry it around with you and do it on a regular basis. The fructosamine test is meant to be an occasional test. So, I guess we imagined that for the most part it would be used in the home.

DR. NIPPER: Thank you, DR. Kurt.

DR. ZAWADZKI: My name is Joanna Zawadzki.

I have a couple sort of technical questions. I can't really visualize the difference between the laboratory

model and the model that would be for over-the-counter use.

DR. BURD: Basically, the test strips are identical. The fructosamine tester for home use is the same as the tester for laboratory use and our intent really is to have the device for sale to the home market, but we wanted to establish that the LXN fructosamine test was equivalent to the laboratory version and that is the reason that we did the studies and did the 510(k) submission for the laboratory use.

The test is meant to be done with capillary blood, so that its use in the laboratory may be very limited.

DR. ZAWADZKI: So this laboratory equipment looks just like the home equipment would look?

DR. BURD: Yes -- John Burd here -- yes, it would.

DR. ZAWADZKI: The other question that I was thinking about as I looked at these clinical study results is that they were obtained at discrete times, at two different times, a whole cluster of results. Have you done any studies of individual meters over time using the meter every two or three weeks to see if the results are stable over time?

DR. BURD: These are studies that are done at LXN. Vivianne, would you like to make a comment on

that?

MS. NOETZEL: Vivianne Noetzel, vice president of clinical and regulatory affairs at LXN Corporation.

We do quality control testing of the meter and of the test strips in the laboratory. However, we have not done those clinical studies out in the field. So, the test itself and the test strips -- the meter and the test strips have been tested as a quality control measure at the company.

DR. CEFALU: I can comment on the use of the meter -- Will Cefalu -- comment on the use of the meter weekly because our recent data that we did, if I could share that with you, where we did a six week study, where we looked at the same meter and looking at the lab fructosamine every week and looked at the clinical validity and the clinical validity or the changes in fructosamine demonstrated by the LXN meter were comparable to what we got with the venepuncture and the lab fructosamine.

So, on a clinical level, the weekly change was comparable and our CVs were similar between those weeks.

DR. ZAWADZKI: Is there any calibration that the individual person would have to do?

DR. BURD: The OTC fructosamine test is very

similar to many of the blood glucose devices that are on the market. Basically, the meter has a check strip to assure that the meter reads properly and we also have a fructosamine control solution, a liquid control solution, that if there is any question, the user could run a test with this control solution and it has to give a value within a certain range.

This is John Burd responding.

DR. NIPPER: Dr. Cooper.

DR. COOPER: Thank you.

I have three questions. The first question there may not be an answer to, but I would just like to know your and perhaps your statistician's opinion. The purpose is just to help me understand the data that were presented.

In the correlations, the curves, all of the curves had, if you will, a standard across the abscissa and the test, what is being tested on the ordinate, and they all had the same pattern, no matter how you worked it and all the different approaches all had the same pattern and there was sort of a -- the ideal curve would be a 45 degree angle going up and all of these kind of sloped down.

Just for my understanding of the presentation of the data, is there an explanation for that?

MR. KENNEDY: There is, indeed, an explanation for that.

Linear lee squares which was used to fit those regression lines operates under a basic assumption that the x variable is known exactly without measurement error. In clinical chemistry, in clinical diagnostics in general, that is rarely true. So, unlike calibration, the x variable has inherent error.

The effect of imprecision in the x variable is to bias the regression line down. The slope will be lower than it actually should be in truth. The intercept will be higher. That is particularly emphasized when the range of the data is very narrow, such as it is in a couple of the individual sites. That is one of the primary reasons we pool data across sites, to get an adequate range of the data.

However, it turns out that the net effect of that lower slope and the higher intercept is really only appreciated when you use that regression equation to estimate the bias at the various concentrations. So, even though that regression is, indeed, biased slightly downward with the intercept bias slightly upward, the net effect in terms of estimated bias is quite small across the range.

So, that is why you see those lines being lower than 45 degrees, but the net effect is still lee squares.

It is still the best fit line for minimizing the amount of error in the line direction. And we see this all the time.

It turns out we go to more extraordinary efforts to change those lines and get a better estimate of the true relationship if, indeed, the estimated bias turns out to be clinically unacceptable. It wasn't so in this case so we did not go to the extraordinary efforts of using some of the other methods that are presented by NCCLS.

DR. COOPER: Thank you. That was very helpful.

DR. NIPPER: And you are, of course --

MR. KENNEDY: I apologize. This is John Kennedy.

DR. NIPPER: Thank you.

DR. COOPER: Thank you. That was very useful.

The participants in the studies, I didn't see the ages. Do you know the distribution of ages of people? And I am particularly interested in the number of people over 65.

DR. BURD: I will differ that question to Vivianne Noetzel, our VP of clinical and regulatory affairs.

MS. NOETZEL: I have an overhead that will show the distribution. This was also included in the 510(k) in

the last portion where we have the questions from the FDA and you can see the age distribution right there.

DR. COOPER: Thank you.

My final question, if I may, I understand, although I have no personal knowledge, that acute phase reaction proteins can interfere with tetrazoline(?) calorimetric tests. In other words, apparently when people get ill and they produce acute phase reaction proteins, it will interfere with similar type tests. Have you explored that with this particular test?

DR. CEFALU: We have some unpublished data, where we did a tetrazoline test in acute MI patients at the acute event and after they were stabilized and showed no difference. That is just our unpublished observations with that.

My name is Will Cefalu.

DR. NIPPER: Thank you, Dr. Cooper.

Dr. Goldsmith.

DR. GOLDSMITH: Thank you. Barbara Goldsmith.

Actually, Dr. Cooper raised the question that I had and that had to do with the distribution of ages, particularly in children.

Also, to this, he said that with children who

obviously are more labile, particularly when they are first diagnosed as having diabetes, you would want to know what their control is. I wanted to know if you had done any -- I didn't see in the data, other than five -- I think you had an n of five less than 20 years old, but, of course, I don't know how old those children were.

Have you done children? If you haven't, are you planning to? And would you exclude suggesting that children should be -- should have your test performed in your insert?

DR. ETZWILER: The studies that we -- Don Etzwiler -- the studies that we conducted were strictly utility studies of is this acceptable to you, do you understand the concepts with patients. We have not done the clinical studies.

DR. CEFALU: We haven't done the clinical studies with the LXN fructosamine but we have done clinical studies with the lab fructosamine, in fact, in a diabetic camp setting, again, looking at finger sticks and five times per day over a week and that showed that the fructosamine actually did correlate quite well to the overall average glucose that week and over the two week diabetic camp, there was showed a reduction in improved glucose control. There was also an improvement in the lab fructosamine.

But I haven't done it with the over-the-counter fructosamine.

DR. GOLDSMITH: How old were these children?

DR. CEFALU: These children ranged in age from about six to about sixteen. This data was presented in the American Journal of Medical Science many years ago.

DR. GOLDSMITH: Do you feel then it would be important to do these same studies with the over-the-counter?

DR. CEFALU: Well, we showed that the clinical validity in pediatrics was comparable to the same that we saw in adults. I can just talk on the clinical validity and we showed no difference and no uniqueness in the pediatric population, compared to the adult population.

DR. NIPPER: Thank you, Dr. Goldsmith.

I have a couple of questions and maybe you could help me understand and make sure I haven't misunderstood how the test will be used.

When you open your jar of strips, Dr. Burd, there is in a sense a calibrator or a lot identifier strip in that jar. In other words, explain a little more to me about how a person would actually log into the system and identify which lot is being used and so forth.

DR. BURD: Again, the design of the LXN OTC fructosamine test is very similar to many of the blood glucose testing systems. Basically, every lot of strips will have a code number and the code number on the box and on the bottle would have to be entered into the LXN meter to establish the proper code for that test. So, it is very similar to the blood glucose testing systems.

DR. NIPPER: Okay. Do you key that lot number in every time you use the system or just once when you key in that lot?

DR. BURD: It basically stays in until you chance it, similar to the blood glucose.

DR. NIPPER: So, you could potentially have a new lot of strips and not key the new lot number in and still get numbers?

DR. BURD: That is a possibility. There is no fail-safe. Again, it is similar to some of the other blood glucose tests.

DR. NIPPER: How many lots of strips roughly have you made now and what kind of lot-to-lot variability would be introduced if a user at home made that mistake?

DR. BURD: We are now up in the twenties of lots of product and basically the results from lot-to-lot are

very similar. I cannot give you a quantitative answer on what that would be, but all I can say is that the standard curves from lot to lot have been very similar with the materials we have made to date.

DR. NIPPER: You can understand the motivation behind my question. I am looking for the worst possible case where somebody would forget to enter it or just be lax or something like that. Would it actually hurt them? So, that is the motivation for my question.

That is all the questions I have for now.

Dr. Rej.

DR. REJ: I have a couple of remaining questions.

I am curious if there have been any studies done with diabetics, who are monitoring fructosamine over a period of time. Has there been any perception on the part of those diabetic patients that daily monitoring of glucose is now less important because they have this sort of average — monitor of the average glucose level over a period of time?

DR. BURD: Well, again, our company intent and our labeling indicates that patients should not -- you know, they should basically do the testing that is instructed to them by their health care professional. This is John Burd

speaking.

So, again, we see the test as totally complementary to the glucose --

DR. REJ: I am aware of your recommendation but I am curious as to whether those studies have been done, whether any of your physician consultants have had any experience with patients, whether they actually see that that might happen.

DR. CEFALU: I can only render an opinion that I don't -- in the patients that we use it on, I have not picked that up, that they feel that glucose monitoring is any less important.

DR. REJ: So, you don't see that as a --

DR. CEFALU: My personal opinion, no.

DR. REJ: In the response to an earlier question, it is my understanding that the over-the-counter product is identical to the laboratory product, the actual meter?

DR. BURD: Yes.

DR. REJ: That wasn't clear from the submission that they were, in fact, identical. That being the case, I see from your overall summary data that you have excellent coefficients of variation both for professional and patient perform testing.

The sort of scatter that I see in comparing them, the over-the-counter product, which is the same to the professional product, seems to me a little bit large when you look at coefficients of variation of 2 percent and we are basically comparing apples to apples not apples to oranges. I am wondering if you could give me an idea of why this scatter seems a lot larger than I would if I was comparing identical products.

MR. KENNEDY: John Kennedy.

Yes, it is. The variation that we reported is within subject variation, which is really the operative variability that we would expect within a subject using this test over and over again. The variability that you observe in the method comparison data is a combination of two factors. First of all, it is a sum -- an adjusted sum of the error in both x and y, because we were using the professional test as x and the participant lay user as y. So, the scatter is going to be somewhat greater because of the combined effect of both of those.

Also, it is between patient variability and finger stick variability. When you take the finger stick data, there is going to be a sample bias introduced, a small sample bias, hopefully. And that is what the net effect is.

That will be different every time you take a finger stick from a different patient or the same patient.

We have measured the within subject variability -that is the data presented at the end -- the 2.6 to 6.6

percent. The method comparison result combines all of the
variabilities, the matrix effects, sample effects, finger
stick effects and the joint error of the two. That is why
you see greater variability in that data.

It is quite similar to the data we see for finger stick data and the glucose monitoring.

Does that answer it?

DR. REJ: You provide some insight as to why there is a much larger variation but I -- it still seems to me that the variation now that I know that the over-the-counter product is, in fact, identical to the professional product, I would have expected it to be better, based on the precision data.

You believe that all of those differences can be accounted for that sample, the sampling variation?

MR. KENNEDY: They all come into play. You can't simply take the within subject variability and extend it to what is likely to happen over many subjects, over many sites, many samplings. Again, these are all first time

samplings from each of the users.

Yes, the scatter is higher. I can't address why it is. We haven't separately measured each of those. What you see, a method comparison experiment, essentially combines everything, all of the sources of error product are allowed to influence what you see there and that is the net effect of all of those without an attempt to separate them into their components.

DR. REJ: One final question.

How did you go about determining the recommended reference values for this system? And can you clarify for me what they are?

DR. BURD: Well, again, we rely upon the history of -- this is John Burd speaking -- the history of the fructosamine, the data and the predicate devices. The Roche method, one of the predicate devices that we used basically looked at a large number of normal, non-diabetic patients and the range for fructosamine is below 300. It is in the 290 micromolar range. It is the upper limit for non-diabetic patients.

In our LXN laboratory submission, we also performed similar studies and found a similar range. So, 300 is kind of a reasonable sort of breakpoint between

normals.

DR. REJ: Maybe you can help me on page 37 of your submission, you have reference values of 1.8 to 2.7 millimolar.

DR. BURD: When we did the laboratory submission over a year ago, basically at that point we were using a correlation to the Sigma method for measuring fructosamine and the units for the Sigma method are in millimolar versus the Roche method and the Berringer Manheim are in micromolar. As it turns out, there is a relationship there of about a factor of 100.

So, I don't recall the number -- you just told me the millimolar value, again, is correlatable to the Roche micromolar value.

DR. REJ: And you don't think it would cause -- I am well aware of method-to-method differences and problems in calibrations. I suppose for some things that is not definable as fructosamine, which is sort of a catchall for a large number of anilides, but having these widely reference values from one system to another for individual patients, is that a problem?

DR. CEFALU: Can I address the -- the fructosamine method he first reports were up to 2.7 is what we consider

the first generation and there have been numerous changes in that assay in addition to how it is standardized through incorporation of uricase(?) in the assay to overcome some of the problems, where the second generation, I think, is what is most commonly used now.

I don't know if anyone that is currently measuring

-- and I would agree with John that -- we actually did some

of those reference range studies for Roche in over 250

patients and the upper limit was about 285 to 300 micromole,

as what you are seeing in the fructosamine.

So, the range reported -- the suggested range for the LXN is, indeed, what is comparable to the second generation fructosamine, which is now what is used in this country. It is not the first generation.

DR. REJ: Then it has been superseded by a new calibration procedure.

DR. NIPPER: Thank you, Dr. Rej.

Dr. Boughman.

DR. BOUGHMAN: Thank you. Joann Boughman, University of Maryland.

I would like for somebody to summarize for me because I am just a little bit confused -- some of these devices have been measuring plasma levels of fructosamine,

some serum levels, but the OTC device that you are proposing is on capillary whole blood. Am I correct there?

DR. BURD: Yes.

DR. BOUGHMAN: And it was the Roche device that uses serum and the LXN lab device and OTC device, both measure whole blood levels?

DR. BURD: John Burd. Yes, that is correct. Would you like me to give a little bit of a --

DR. BOUGHMAN: Could you just summarize that because we have on the axes sometimes it is whole blood versus serum, plasma versus plasma and so on. If you could summarize, it would be helpful.

DR. BURD: Sure. When we did the initial correlation of the LXN test to the laboratory test for the laboratory 510(k), basically we looked at the comparison of the LXN test with blood and plasma and compared that to the laboratory reference method, which is a serum or plasma test.

We then went on to do our OTC studies. We basically compared finger stick blood correlation to the Roche method, which uses a venepuncture sample and plasma from the venepuncture sample. So, it is the LXN capillary versus the venous Roche plasma method.

DR. BOUGHMAN: Okay. Thank you.

I have a few questions on the labeling and some of the information that is either there or, in fact, not there.

In the LXN lab device inserts, there was a reference to fasting blood not required. Nowhere in the materials that would be given to a patient does it make any reference to whether the sample should be collected fasting, non-fasting, whether it makes a difference or not.

Were you planning on giving any advice with regard to that or any recommendations?

DR. BURD: Well, again, historically the fructosamine value -- this is John Burd speaking -- the fructosamine values do not change like blood glucose test results, so that it really does not matter if the blood sample is from a fasting sample or a non-fasting sample.

DR. BOUGHMAN: It seemed to me that it might be helpful to so state somewhere in the labeling.

There is also a question -- and I am glad somebody raised the issue about the test strips and the length of time they have for shelf life -- there was also an incongruous set of statements in the inserts where the recommendation is to do the fructosamine OTC test once every week to two weeks; yet, in the care of the meter, it states

you are supposed to clean the meter every week.

Does this mean if you are only testing every two weeks that you are supposed to clean it more than you actually use it or do you -- there is a -- could you comment on the incongruous statement?

DR. BURD: This is John Burd.

Yes. If the user is not using the meter, then there would be no need for them to clean the meter. So, that is something that we can attempt to clean up in the labeling.

DR. BOUGHMAN: Okay. There was another reference in the labeling somewhere that there were no studies done or there was no knowledge of, I guess, interference due to pharmacologic or pharmaceutical substances. Has any of that testing been done or would the statement remain the same?

DR. BURD: This is John Burd. I think I will defer that question to Vivianne as far as the interfering substances studies that were done with the device.

MS. NOETZEL: I think you are referring to in the lab fructosamine, where we stated that those studies had not been done. They still have not been done.

DR. BOUGHMAN: Okay.

Then I have one more question there -- well,

actually two more questions. On the insert on page 16, it says that if your blood sugar protein test result is higher or lower than you think it should be, you should do three things. First, you check the test strip. Then you check the meter test window and, thirdly, you repeat the test.

Does that mean that a patient should collect a new sample and repeat the test or is it only the use of another strip? It would be a new stick?

DR. BURD: John Burd. Yes, it would be a new finger stick.

DR. BOUGHMAN: Okay.

And the last question has to do with the materials with the packaging as well on the limitations and precautions and recognizing that this is detail beyond usual human use studies or human factors studies, I had some concern about some of the vocabulary used in the limitations and precautions for an OTC device, including the terms "neonatal," "whole blood hematocrit" and "high fatty substances," with indicated levels that a patient might or might not know about themselves.

I wondered if there had been any if not systematic study, any questioning of patients about knowledge of such vocabulary terms.

DR. BURD: Again, I will defer that question to Vivianne Noetzel.

MS. NOETZEL: When we were starting our blood glucose test, we worked with one of the FDA reviewers and she recommended that verbiage.

DR. BOUGHMAN: Okay. Thank you.

DR. NIPPER: Before you start, my ticker says we have got about four minutes before we start another presentation and then, just so the rest of the panel doesn't feel neglected, we will come back to you and start with you when the open panel meeting comes up.

Dr. Clement, would you like to go ahead?

DR. CLEMENT: Sure. Or I could defer my time if there are any burning questions.

DR. NIPPER: Dr. Harrington Falls.

DR. HARRINGTON FALLS: Beverly Harrington Falls.

I just had a question regarding the over-the-counter versus prescription use. In my experience, patients will borrow family members, monitors and do all sorts of things trying to self-diagnose. Is there any consideration in warnings over use of the monitor if no diagnosis has been given?

DR. BURD: I think I will again defer that

question to Vivianne Noetzel.

MS. NOETZEL: Vivianne Noetzel.

If you notice in our expected results, even if they were to test, they would not know what their correct range for them is. So, they would still have to contact their health care professional.

DR. NIPPER: Well, I have advice that we can go ahead and not neglect the rest of our panel. I will not be like Father Time today.

Dr. Clement, you have been very gracious to defer, but we will come back to you and ask for your questions now.

DR. CLEMENT: I can't side step this one then, I guess.

DR. NIPPER: If you do not have any questions, we won't fire you off the panel if that is the case.

DR. CLEMENT: Oh, no, I do have questions.

One of the questions was actually a follow-up on your comment on the labeling and it has to do on page 13 with the labeling about what to do -- what test result will you get when you test your blood. Obviously -- and the wording is extremely conservative. Basically, it just says that your test results should fall within a target range recommended by your health care professional.

The issue that I have is that since most health care professionals, not just endocrinologists and folks interested in diabetes, but the folks that primarily see these patients, which are the primary internists, pediatricians and so forth, they don't have any idea what the normal range of fructosamine is. What I see is that these folks — there is going to be a tremendous amount of confusion based on the labeling.

I understand the reason for that. As a company, you want to be very conservative and not try to actually extrapolate that this number equals this average of a blood sugar, but I foresee that when this -- if or whenever this gets out, available in the hands of the consumer, there is going to be a tremendous amount of confusion, there is going to be a tremendous amount of phone calls to the physicians' offices and the physicians' offices won't know how to respond to it because they have generally been using AlCs and not fructosamine.

Can you comment on that? And how you would get around that learning curve, so to speak, between the consumers and the practitioners?

DR. BURD: Basically, again, it is -- I think it may have some similarities to the early days of the home

blood glucose testing, where it took time for people to become educated as to what the correct sort of timing of taking the test and what the results should be.

This is John Burd speaking. We actually -- in the literature, there is a correlation between blood glucose -- average blood glucose results and hemoglobin AlC results, which came out of the DCCT study and there is published literature that correlates fructosamine values to hemoglobin AlC results. So, in fact, some of our educational literature does have a nomogram that compares average blood glucose to fructosamine results to hemoglobin AlC results. We actually have an overhead of that, if you would like to see what that looks like.

DR. CLEMENT: I think that would be helpful for the audience.

DR. BURD: Okay.

Then, again, this nomogram shows on the left side here the glucose in milligrams per deciliter, the average blood glucose and the hemoglobin A1C results on the right hand side and then the fructosamine values that correlate with those sorts of values. So that in a management program if -- so that you can see here that fructosamine values are correlatable to both average blood glucose and hemoglobin

A1C.

DR. CLEMENT: That is very helpful. I would recommend that some type of labeling or that nomogram actually be put in the patient handouts because I can see just tremendous amounts of confusion and the primary care physicians wouldn't know how to deal with it.

My second question has to do with not your interfering substances so much but on the earlier and maybe in the first generation fructosamine assays that Dr. Cefalu was alluding to did have falsely elevated, falsely lower numbers with situations of dispronemia(?), low albumin states, which we see a lot of in folks with end stage diabetes, particularly when they are associated with nephrotic range proteinuria. I can use more medical terms, but there are alterations in the protein in the blood that can interfere with the assay, on the earlier assay.

Have you found that with this assay? Again, I did not sit in the hearing for your original professional --

DR. BURD: Dr. Cefalu would like to respond.

DR. CEFALU: Actually, that is one of the major advantages of this second generation based on the standardization. There was some concern with the first generation assay that hypoproteinemia or the albumin level

actually did affect the measure.

We have studied that with both the first and the second and because of the modifications in the second generation, particularly with the standardization, that we did not feel that there was a protein effect. We reported this in elderly patients where proteins were as low as 2. We didn't see that a correction for albumin was necessary. This is for the second generation.

This is, I think, as far as I am concerned, one of the advances between the first and second generation, which is currently what we are measuring.

DR. CLEMENT: Okay. Thank you very much.

DR. NIPPER: Thank you, Dr. Clement.

Do you have any other questions, Dr. Harrington Falls?

DR. HARRINGTON FALLS: No, thank you.

DR. NIPPER: Ms. Rosenthal.

MS. ROSENTHAL: One of the advantages of being so close to the end is that most of my concerns have been addressed already. Dr. Cooper addressed my concern about the slope of the regression line. But I was just curious and -- John Kennedy, I believe his name -- did explain that. If you reversed the axes, if you had the patient say or the

-- yes, the patient as your x axis instead of your y and vice-versa, would we see the same slope on that line or would it be reversed. Would we see a steeper slope?

MR. KENNEDY: John Kennedy.

I don't know what the slope would do if you reversed the axes. We are so conditioned to think of the test method as the y axis and the comparative method as x. What would happen, the slope would be higher, certainly higher. It would also be biased downward because, obviously, even when you reverse the axes, then your new x axis is still subject to error in measurement.

So, it would be lower than it really should be to get at the truth. But my guess is it would be a higher slope because if you multiply the slope of x on y times the slope of y on x and take the square root, you get the correlation coefficient. So, it certainly would be higher.

MS. ROSENTHAL: Okay. And I had one other question.

One of the last slides that you showed us was a precision study of ten participants with very small coefficients of variation. Could you tell us a little about those ten participants? Were they trained? Were they not trained? Were they random?

DR. BURD: Again, I will defer that question to Vivianne.

MS. NOETZEL: Vivianne Noetzel.

And, yes, these are patients that were brought in. They were trained. They did the control solution and once we saw that they could do the control solution, then we asked them to finger stick five separate fingers.

MS. ROSENTHAL: Thank you.

DR. NIPPER: So, this is a between finger CV.

MS. NOETZEL: That is correct.

DR. NIPPER: Dr. Habig.

DR. HABIG: Thanks. This is Dr. Habig.

I have two questions that relate to the code number on the meter. What is the range of code number possibilities in the electronics of the meter?

DR. BURD: There will be 24 code numbers possible.

John Burd responding.

DR. HABIG: And you said earlier you made about 20 lots of test strips. Can you or someone, John, tell me what the range of code numbers required for that 20 lots has been?

DR. BURD: This is John Burd responding.

The final coding procedures are still -- we are

still finalizing that. So, I cannot tell you that specifically at this moment.

DR. HABIG: But as you test those lots, you must have to assign a code number. Isn't there some range of numbers that you already know?

DR. BURD: Our testing basically involves testing the raw reflectance values of the different lots. So, we are still working on looking at lot-to-lot variability and then, of course, we will expand beyond the lots that we have currently made to encompass lots in the future that would still give acceptable results.

DR. HABIG: One final question on the lots.

How many lots were used in the total set of clinical trials that you ran?

DR. BURD: I will let Vivianne respond to that.

MS. NOETZEL: Two lots. One lot was used in June and one lot was used in the November/December.

DR. HABIG: Okay. Then the final specific question. What were the code numbers on each of those two lots?

MS. NOETZEL: Specifically, it was 6 and 7, but I don't know if that really answers your question.

DR. HABIG: Yes, it does. If one was 6 and one

was 7, that answers my question.

Thank you.

MS. NOETZEL: Thank you.

DR. HABIG: Then I have a very specific suggestion, I guess, in the labeling. On page 15, you describe sample collection in a blood straw, but step 4 says place the drop of blood on the strip, but you really don't explain whether you have to do something with the blood straw, which is a capillary tube, I guess, to create the drop. So, the first time you talk about putting the capillary blood on the strip, you call it the drop. But it isn't a drop. It is a blood straw full of whole blood.

So, I suggest you clean that up a little to explain how a drop is actually achieved.

DR. BURD: This is John Burd.

We definitely will. It will be clear in the package insert with pictures and so on, how it should be done.

DR. HABIG: Okay. That is great.

That is all. Thanks, Henry.

DR. NIPPER: Thanks.

I am going to exercise the chairman's prerogative to rap up here for a minute to see if there is one follow-up

question that have any of the panel has and then we will take a 15 minute break before the presentation by the FDA.

Dr. Rosenbloom, do you have one question?

DR. ROSENBLOOM: Yes. In response to question 14, provide data to demonstrate the effective sample volume, et cetera, the sample volume study, there were two, four, six - there were a dozen various levels of volumes and of those dozen results, there were three that were outside of the 10 percent target fructosamine level. That data seemed to be inconsistent with the accuracy seen elsewhere.

Could you explain that?

MS. NOETZEL: Yes. The straw has been calibrated to deliver a certain amount of volume. So, you would not observe those lower volumes. What we were trying to show there, upon FDA request, was if you were to go and actually only put in half the volume, then you would see a problem, but the straw has a line on it that you must draw the letter line.

DR. ROSENBLOOM: So, what you are saying is that low volumes will affect it, but high volumes will not?

MS. NOETZEL: That is correct.

DR. NIPPER: Thank you, Dr. Rosenbloom.

Does any other member of the panel have a follow-

up question?

Yes, Dr. Kurt.

DR. KURT: Urinary tract infections are very common among diabetics and recurrent urinary tract infections. With such infections, the person is febrile and frequently there are cytokines circulating in the blood under such circumstances. Have you any indications of your test strip functioning under these circumstances and what influence, if any, with the temperature the cytokines produce?

DR. BURD: This is John Burd.

No, we have not done any studies directed specifically to that.

DR. CEFALU: Getting back to the question that was asked earlier about acute phase reactives and I said all we have is just some unpublished observations that an acute event, like an acute MI, when followed a week or ten days later, there was no difference. But we haven't looked at any other.

Will Cefalu.

DR. NIPPER: We can tell because we recognize that accent.

Any other questions?

[There was no response.]

Well, I want to thank the representatives from LXN for being so forthcoming about the information.

We will promptly reconvene at 10:10 according to my watch and begin open committee discussions at that point. I am sorry. Pardon me -- FDA presentation.

[Brief recess.]

DR. NIPPER: We are ready to reconvene. I said 10:10, but we are on FDA time here. So, I think when the FDA is ready, we are ready.

Patricia Bernhardt MT(ASCP), scientific reviewer, is at the podium and ready to start. Go ahead.

Agenda Item: FDA Presentation

MS. BERNHARDT: Good morning, ladies and gentlemen and distinguished panel members.

My name is Patricia Bernhardt. I am a scientific reviewer in the Division of Clinical Laboratory Devices.

The device we are discussing today is the first of a kind over-the-counter test system for measuring fructosamine.

First overhead, please.

FDA review of the premarket notification was performed by the following review team: Ann Hawthorne, chemist; Augustine Gonzalez Risia(?), medical officer; P.C.

Liu, mathematical statistician in the Division of Biostatistics, and myself.

In addition, consultation was sought from a human factors specialist in the Office of Health and Industry

Programs, as well as several diabetologists in the Center for Drug Evaluation and Research.

In a premarket notification, FDA's mission is to determine whether the data submitted demonstrates that the device under review is substantially equivalent and is as safe and effective as the legally marketed predicate device.

The fructosamine test system proposed for overthe-counter use is therefore being compared to a fructosamine system currently legally marketed for professional use.

As you recall, fructosamine is a generic name for plasma protein ketoate(?). The name "fructosamine" reflects the structure of the moiety form by glycation of the protein. Analogous to glycated hemoglobin, fructosamine is used as an index of glycemic control over time. FDA has approved numerous premarket notifications for fructosamine assay for use in clinical laboratories. The first such fructosamine assays for use in the clinical laboratories was approved in 1987.

Today we are asking you to consider an over-the-counter fructosamine tester. FDA has guidance documents for use in evaluating home use diagnostics entitled "Assessing the Safety and Effectiveness of Home Use In Vitro Diagnostics: Points to Consider Regarding Labeling and Premarket Submissions," which was published in 1988 with input from industry, professional groups and members of our panel.

This document points out that at least two issues are important in evaluating the transfer of testing technologies from the professional to the over-the-counter status.

First, the device used in the hands of lay users must provide results, which are substantially equivalent to those obtained in professional use settings and, thereby, support the ability of the ability to provide successful results to the lay user at home.

Secondly, the benefits of use of the device in the over-the-counter setting must outweigh the risks. We are seeking your input today on both of these questions as they apply to this fructosamine assay.

FDA has cleared a number of tests for over-thecounter use, including pregnancy tests, ovulation predictor tests, glucose meters and cholesterol tests. In making these determinations, we have considered the anilide itself, clinical interpretation of normal and abnormal values and the action or actions that may result in generation of test values at home.

Issues of importance in risk/benefit analysis with these anilides have included a consideration of the ways in which patients' self-management is handled, the likelihood of benefits of over-the-counter use, convenience, patient knowledge and the likelihood of harm to the patient as a result of potential misuse of information.

They also have submitted data for 300 more subjects, compared with results obtained from the device simultaneously on the same subject by a health care professional. These results were also compared with simultaneously drawn venous samples from the subject as made with the predicate device in the clinical laboratory.

Bias decisions and correlation results obtained in these studies were presented by the sponsor and are defined insufficient for the device, although this is relative performance since the assay is to date not well-standardized.

Device labeling advises patients to confer with

their doctors and not to act on results on their own. The relationship between glycemic control and fructosamine levels is presumed based on our knowledge of the literature, but not specifically defined in the submission.

Although home measurement of glucose is now a well-established practice with clear potential benefits to users, the potential benefits of home measurement of fructosamine has, to our knowledge, not been clinically demonstrated. FDA is uncertain how to evaluate the relative risks and benefits of this factor.

In the course of its review, FDA has considered the stability of a mechanism intermediate between professional use and over-the-counter use for marketing this product. That is, for home use but by prescription. This would allow increased access to the test by patients but would allow continuous physician-directed supervision of testing results until the risks and benefits of use in this study are better defined.

In summary, FDA raises several questions for consideration by this panel.

If there are reasonable expectations that patients self-management will be enhanced by the device, is there a likelihood of benefit from over-the-counter use as reflected

in enhanced convenience, patient knowledge and/or a sense of empowerment to take action?

Is there a likelihood of harm to the patient as a result of potential misuse of the information in a non-prescription setting?

Is the performance of this device in the hands of the lay user appropriate to consider the device substantially equivalent to the predicate device? Are other studies or other analyses of existing data also needed?

Is the use of the device in the over-the-counter setting substantially equivalent, that is, as safe and effective as the use of the device in a prescription setting? If the product is considered substantially equivalent, do you have any suggestions for enhancing the labeling of this product? In particular, we recognize differences in the way quality control is intended for the over-the-counter product versus the same product in professional use.

We would appreciate input from the company and the panel on these questions. We are asking that you advise FDA on these considerations and provide any additional comments to the staff.

Thank you for your attention. My colleagues and I

would happy to answer any questions at this time.

DR. NIPPER: Thank you, Ms. Bernhardt.

At this time, the panel members should have noticed by now that these questions that were read by Ms. Bernhardt are in order at the end of her handout, beginning with page 1, LNX fructosamine test system, FDA questions. What I would like to do at this time is, if there are no questions for Ms. Bernhardt -- and I will certainly open that up in just a second -- is to go around the horseshoe question by question and ask for panel input to the FDA at this time.

In lieu of voting, this will be our way of formally advising the FDA of our opinions on these particular questions.

Agenda Item: Open Committee Discussion

This is an open committee discussion. This portion of the meeting is, of course, open to public observers, but it is for the committee to decide whether these observers may participate at the request of the chairperson. So, if we have questions for the FDA and for or for LXN itself, we have the right to ask those questions.

First of all, before we begin with the specific questions, are there any questions for Ms. Bernhardt and her

colleagues?

Yes, Dr. Cooper.

DR. COOPER: I just have a very quick question.

If the FDA decides that this is approved for at home, but prescriptive use, how long is that -- when could that be changed? What normally happens in that event?

DR. GUTMAN: If that was a decision, if that was a recommendation and the FDA were to accept that recommendation, that would be the way this particular 510(k) would be cleared and that would be a limitation on the use of the product under this 510(k).

At a point in the future, if the company wished to expand that claim on new studies or experience or the literature or anything else, they would need to come back with a new 510(k). Depending on the circumstances of the data set and the nature, that might or might not go back for panel input.

DR. NIPPER: That was Dr. Gutman from the FDA.

Any other questions for Dr. Gutman or his colleagues?

[There was no response.]

Okay. Well, the first question -- hearing none -- the first question that we were asked as a panel to

consider, is there a reasonable expectation that patient self-management will be enhanced by this device?

Dr. Rosenbloom.

DR. ROSENBLOOM: I am pleased with the direction the discussion has gone because that was an earlier question I had but I thought it should be put off. In view of the fact that we are dealing with a patient population that is largely treated by non-experts in diabetes and the -- I had considerable question about over-the-counter use of this product. I think there is an enormous educational effort that needs to be made.

We even see -- I hate to say old diabetologists, being one of them, but we even see people with training before the glyco hemoglobin era, who do not routinely do glyco hemoglobins on their diabetes patients, even though they are touted as diabetologists. So, I think there is -- the answer to the question, is there a reasonable expectation that patient self-management will be enhanced by this device, is -- the response has to be qualified and interpreted.

There is more than reasonable expectation, I think there is a good expectation under the supervision of a diabetes team or an informed non-diabetes specialty nurse,

physician, whatever, if it is within that context. I cannot envision how a patient could go to -- blood glucose values, in contrast to what was said earlier, there wasn't much of an education required to teach people what a normal blood glucose was. Certainly there was in terms of target blood glucoses for people with diabetes.

Once we had a means of monitoring blood glucose, we could adjust our targets to be much more realistic than we were doing with urine testing and vague -- and symptoms. But we knew -- everyone knows what a normal blood glucose is. Nobody knows what a normal fructosamine is. By "nobody," I mean, present company excluded, after this morning.

But I really have difficulty responding to this question without the very large qualification of an educated health care provider working with the patient. So that I would strongly favor an alternative to over-the-counter use because I really do not see how it can enhance self-management without the involvement of the health care -- of the informed health care provider. So, you have got a couple of very important steps in there that would have to be taken.

DR. NIPPER: Dr. Habig.

DR. HABIG: I think it is important to remember that the panel's advice to the FDA gets, you know, received by the FDA and then FDA ends up making a judgment. This question, which the panel is now debating, is on, I think, a fairly thin line about clinical utility and those of us in industry worry sometimes about the incursion of FDA's reviews into clinical utility when, in fact, FDA in this case is looking at substantial equivalents to a legally marketed device.

I just want to remind the panel that we are not here looking at clinical utility. We are supposed to be looking at substantial equivalents.

DR. NIPPER: But I understand we are looking at safety and effectiveness as well. So, the question, as I understand it, before the board -- and I would like -- before the panel -- and I would like the FDA professionals to correct me -- is that we are also looking -- we are not only looking at analytical equivalents or substantial equivalents. We are looking at the safety and effectiveness of this device as proposed for over-the-counter use, as an over-the-counter use.

DR. GUTMAN: That is correct. I assure you if it were not for the over-the-counter use issue here, we

wouldn't be at this panel meeting.

DR. NIPPER: So, as I understand this question, what we are trying to find out is if we put this in the hands of patients over the counter, is there a reasonable expectation that patients will benefit to a greater extent than they would be placed at risk? I think that is a reasonable -- I think that is an appropriate translation of that question.

So, let me return to Dr. Rosenbloom and in a word is your vote "yes," "no" or "maybe" on this?

DR. ROSENBLOOM: With the present package insert, without any values, without any statement that here is a package that you need to take to your physician and make sure he understands it and understands the numbers that you are going to get and is going to read those numbers, the answer is "no."

DR. NIPPER: Dr. Kurt, you don't have to curt.

You can expand on that a little bit. I am sure you have
never heard that joke before, just like I have heard "little
nipper" before.

DR. KURT: Of course not.

Tom Kurt, Dallas.

I think that the marketplace more or less will

allow the manufacturer to properly warn the purchaser of this device from the standpoint of the manufacturer protecting its own liability. This is not necessarily a substitute for a glucose measuring device and even though it is the newest thing, it is not necessarily to take a glucose measuring device's place in the day-to-day management of the patient's condition.

Consequently, I think in the labeling and in the marketing of the device that, providing this is explained, that, indeed, patient management will be enhanced. So, I would tend to be in favor of this device from the standpoint of being an over-the-counter consumer used device with the understanding, of course, that the manufacturer is going to protect itself, but not necessarily suggesting that this is a substitute for glucose monitoring.

DR. NIPPER: Thank you.

Dr. Zawadzki.

DR. ROSENBLOOM: Excuse me just a minute. Did we say the same thing? I think we said the same thing.

DR. NIPPER: I think you did, too. Sometimes it is hard to say.

DR. COOPER: No, you didn't. May I correct that
-- I don't think he said the same thing. I think Dr.

Rosenbloom, you felt -- my interpretation of these remarks, and I am only doing this because you can then correct me to make sure that what you want to say is -- comes out that way, the way you want it to.

Dr. Rosenbloom, you said that you would vote "no" right now, the way it is packaged. And you would vote "yes."

DR. ROSENBLOOM: But I understood Dr. Kurt -- this will be interesting. We are interpreting each other's comments -- I understood Dr. Kurt to say that he expected the manufacturer to package this in such a way that it would include the stipulations that I required to consider it a self-management improvement. That was the common ground I thought we were on.

DR. NIPPER: Okay. Anything you would like to add, Dr. Kurt?

DR. KURT: The point that I was -- the package could be labeled as new, you know, such as your new soap suds, but it is not a substitute for glucose testing nor should it be marketed as a substitute for glucose testing. It is more in the chronic management of the control of the patient, rather than the acute day-to-day management.

DR. ROSENBLOOM: But do we still want to give the

patient the opportunity either through marketing or whatever to purchase this device and play with it without discussion with the health care professionals, who need to help them interpret it and need to be educated about the value of the results?

DR. NIPPER: Okay. Let's move on to Dr. Zawadzki and see if we can complicate this further.

DR. ZAWADZKI: I interpret this question on two levels. The first way it appears to me is that from my perspective, I don't think this -- I don't think measuring blood -- any method of measuring blood glucose every two to three weeks will improve an approach to measuring blood glucose several times a day, which we encourage many of our more intensively controlled patients with diabetes to follow.

So, if that is the question that is being raised, I don't think we can improve on the current methodology that we routinely use. On the other hand, I think it can supplement some methodologies that we have and I certainly agree that it has to be done in the setting of the diabetes health care team.

Occasionally, we have patients who go out on their own and buy meters that are really inappropriate for their

abilities and similarly I think what we have learned this morning, that this meter -- I think there are certain people who would have difficulty with that or difficulty reading those instructions without reviewing them with someone.

Furthermore, it became very clear that most of us really were unfamiliar with the answers we were supposed to get on this test. So, how can we expect the random consumer to do that without more guidance? So, I do agree that in some implied or imposed way, there has to be an interaction with the health care system to make this methodology, which I think is a real potentially positive one, really worthwhile.

DR. NIPPER: Could I ask you all a question?

Since, according to what I read, a lot of the people that should be monitored by fructosamine or hemoglobin AlC are not currently benefiting from that monitoring as it is currently offered, do you see a prescription device, such as this, correcting that problem or would the over-the-counter use of that go further to correct the problem?

In other words, are we going to be able to reach the people that need the fructosamine assay if this is prescription only as opposed to over the counter?

DR. ZAWADZKI: I think the way I see that quandary is a little bit more complex. I think the reason some patients do not receive chronic measurement of their glycemia is because of lack of physician knowledge or interaction with the physician. I think the people who would be most likely to acquire a meter such as this one are the ones who already come to physician care the most.

So, I don't think that the ones who are not being tested benefit the most from this meter, either over-the-counter or prescription meter. And I don't -- to my mind, over-the-counter or prescription is not the biggest difference. The main issue is involving the health care team and learning about the benefits of the team.

DR. NIPPER: Thank you.

Dr. Cooper.

DR. COOPER: I think I agree with Dr. Rosenbloom,
I think. I interpreted this question, to me it meant that
if patients had this device, would it enhance their selfmanagement. And I interpreted that very narrowly and I
think under certain circumstances, that would be true. I
raise concern -- my concern is that in the extreme case,
such as you just suggested, Dr. Nipper, a person purchasing
this and being completely outside of the health care system,

but purchasing this and attempting to use it on their own, I think that, indeed, would be dangerous.

I would like to find some way in which we can be assured, as your point is, that a person using this does it under close collaboration with their health care provider.

I am not convinced that making it over the counter would assure that.

So, I -- it is hard for me to answer this question as it is stated. I think the device has a great potential to enhance patient self-management, but only under certain circumstances.

DR. NIPPER: Dr. Goldsmith.

DR. GOLDSMITH: Yes, this is a difficult one to answer straight out, as well. It is a "yes, but." I think that does it have the potential, yes, but in terms of physician knowledge, I have to agree with the comments I heard earlier, just on a practical note. In the laboratory we developed this assay. We introduced it. Nobody used it. And that is because many of the clinicians were not familiar with it.

So, we currently don't offer it and that is why.

I would like to reintroduce it. However, I do feel that

education is the key component to this. So, I would be

uncomfortable with its use over the counter without that being a strong component, the physician knowledge of its use.

So, would I expect it to improve patient selfmanagement? Yes, but I would feel more comfortable in a prescription environment as opposed to over the counter.

DR. NIPPER: Thank you.

Dr. Rej.

DR. REJ: I think I have to agree with Barbara's comments, especially the way that the package insert is currently written. It really indicates that there should be a close collaboration between the patient and the physician in the interpreting of the results and, therefore, I think the physician should be involved in the actual recommending of such a device to his or her patient.

So, I would concur with that recommendation.

To answer the question outright, again, I had some concerns -- a question that I asked the sponsor of this device is that would this test be used in lieu of or result in a lessened day-to-day management of glucose. That is still a concern of mine and I think by having this device available by prescription, that would alleviate my concerns about it.

DR. NIPPER: Thank you.

Dr. Boughman.

DR. BOUGHMAN: Thank you.

I would try and answer the question as directly as I could by changing it into an initial statement with a couple of additional sentences added. I would say there is a reasonable expectation that patient self-management in some cases may be enhanced by this device. It would be those patients who are well-informed and understand the relationship between variability and changing blood glucose levels within a day's time or over a few days and longer term measures, such as fructosamine that, in fact, might have their management improved slightly.

However, those in good control anyway might not see an improvement in self-management and those patients who have extremely poor control, this additional piece of information would not add substantial improvement to the management. They would already know by their blood glucose levels that they might not be in good control.

So, as an alternative statement to in individual cases, I would suggest that in the diabetic population as a whole, that, in fact, patient self-management in general would not be substantially enhanced by this device, but in

certain cases, it might be very useful.

DR. NIPPER: Before I move to Dr. Clement, I think as a comment, this question is interesting in that it is phrased in terms of patient self-management as opposed to patient medical management.

Dr. Clement.

DR. CLEMENT: To answer that question from a very objective point of view, we really don't have the data to answer this question. You are basically asking us for an impression of -- basically, a leap of faith based on what we see so far. That is what is tough. That is what is tough about this.

There are some very positive things about this device. I am very impressed by the presentation of the company. I think they have a very good idea of the niche of where this device and the readings, interpretation of these numbers fit into a global management. And from a specialist in diabetes, I am very excited about that because I think in the motivated, quote, unquote, empowered patient it will enhance their control and more data, particularly if it is accurate, which we have seen today, it seems to be substantially equivalent to the laboratory device, I think it would help.

In the perfect world situation, I would like to sit down one on one with every patient getting ready to use this device and actually go over it with them and what the results are expected to show and how I would like to see that happen.

Unfortunately, this is not a perfect world and not everybody has access to an endocrinologist or even a primary internist with specialty training in diabetes. So, that is really an unrealistic expectation. So, this whole issue of how much education does the patient need before they get this device and how much is enough is a difficult one as well because not everybody has access to this.

I think realistically that the company does have a good idea of the education work that is involved and I think it is potentially that they can put enough education materials in with the device and also with education materials to send to physicians, that both can be educated simultaneously.

So, my answer to this question is a qualified "yes." I think it can be done. I think in a subset of patients who are motivated and empowered and want to do the best for themselves, which is actually, I am finding, a very large -- fairly large group of people, it will enhance their

device.

I would like to see follow-up data, though, some type of study of patients using this device at home versus ones not using the device in the home situation to see in an objective type of scientific study whether it actually does help their control. It would be very interesting to see that.

DR. NIPPER: Thank you.

Dr. Harrington Falls.

DR. HARRINGTON FALLS: Dr. Beverly Harrington Falls.

Again, coming in at the end of the loop, many of my concerns have already been addressed. The issues that have been brought up also related to question No. 5, is this device as safe and effective in the prescription as overthe-counter setting.

Just to bring an analogy, sometimes we have teenage girls, who are trying to get pregnant, who will do a pregnancy test every single day, hoping to get pregnant, and that is not what the test is intended for. Again, they are not going to be using this device in a void. They have to coordinate with their health care provider and, in fact, the proposed insert did mention you are not to make any

adjustments in your regimen without expressly being instructed by your health care provider.

And Dr. Boughman's comments were very helpful in that regard. If someone is not in good glucose control to begin with, then this wouldn't substantially improve their self-management.

DR. NIPPER: Thank you.

Ms. Rosenthal.

MS. ROSENTHAL: Well, it is wonderful to say something, considering we aren't really voting and I am a non-voting member, but I --

DR. NIPPER: We value your opinion.

MS. ROSENTHAL: I know. Thank you.

I very much am in favor of this device and I do think it probably should be prescriptive because I think it is something that requires some education. I know Dr. Rosenbloom voiced some concern because he said the public isn't familiar with the values and they are familiar with blood glucose values. But there was a time, of course, when the only thing a diabetic knew was a dip stick that was plus 1, plus 2, plus 3 and plus 4, and they very quickly learned how to use a glucose monitor.

In fact, you react more quickly to a glucose

monitor. Most diabetics will change their insulin administration daily according to the results of their glucose check.

I feel it would -- you know, in the eighties, I think we acknowledged the ability of the patient to monitor themselves with blood glucose monitors constructively. This is being administered the same way, less frequently, but why would we not want to give that diabetic the opportunity to help themselves and to measure the way that they are testing their own blood glucose.

If you have ever lived with a diabetic, you know that waiting for that A1C is like waiting for the results of a final examination. It tells them whether they have been doing well or whether they have not been doing well. I think that it would almost be remiss to not allow the ambitious diabetic to be empowered with a device such as this. I do think it needs -- I would recommend prescriptive because I think it does need education.

I guess that is my recommendation.

DR. NIPPER: Dr. Habig.

DR. HABIG: I think I would be a bit more positive than many of the comments, perhaps, except for Dr. Clement.

I think the clear answer to this question is "yes." The

qualifiers seem to me to be based on a bit of unwarranted concern. Dr. Cooper actually said dangerous. The down side of getting wrong answers or getting uninterpretable information is not very large.

One is not expected to go out and change their insulin based on a fructosamine value. A lot of good medical care in this country has come about because people who have diseases have requested, required, pushed their physicians to learn about things that they thought the physician should know about. A fair amount of advancement in medical care probably came from reading the Reader's Digest.

I am not convinced that it has to be a prescription device that a diabetic's physician has to know about first. I think putting it in the hands of someone who -- well, many diabetics don't like to tell the truth about their glucose values when they see the diabetologist or their clinician and the AlC, of course, has helped that a lot. For those people who are having trouble or perhaps not even want to admit that they are not in as good a control as they ought to be, I think this would give them some home value practical information and that would help them to stop kidding themselves that maybe they are going to be okay.

So, I think over the counter is not a problem and I think it ought to be in the hands of people who would figure it out.

DR. NIPPER: Thank you.

I am intrigued by this device and I enjoyed thinking about how it might be used. I have also been interested in and fascinated by the fact that over the years I have had the same experience when I was director of chemistry that Dr. Goldsmith had, that fructosamine was ignored as a test by many people who you would think would order it on certain patients.

we doing an end run around physicians who are not using the test in appropriate circumstances in patients? And if we do that end run and put the thing out on the market, will the patient pick up on this and use it effectively? What we are asking the patient to do then is in his or her relationship with the physician who is not ordering the test on these 80 percent of the people who are not getting it, if the patient comes and says, Doc, I have got this test result that I got in the drug store, work with me, will we build patient/physician relationships? Will care be enhanced and so forth?

My feeling is that the only way we are going to know this or be able to make an educated guess about this is to have the same kind of trials with good solid physician backing that we did a decade or more ago in self-monitoring blood glucose studies. I do think that there is a good expectation that the patient's self-management will be enhanced by this device. I think we can prove it to the medical community by having it in the hands of educated patients and well-intentioned and educated specialists in diabetes care. We can show that it works, that it does enhance patients' self-management.

I would be happy to see that done as a precursor to over-the-counter sales of the device.

Yes. Make it brief, please. We have some more questions to go through.

DR. ROSENBLOOM: How realistic -- and this might be addressing another question -- how realistic is over the counter anyhow since we have very patients buying meters over the counter because they are not paid for by third parties unless we write a prescription?

DR. NIPPER: I don't know and I don't think that this panel is going to be able to tell that.

Let's move on to question No. 2, which essentially

feeds on what I just said. I am going to start at the other end of the horseshoe, Dr. Habig. Is there a likelihood of benefit from over-the-counter use as reflected in enhanced convenience, patient knowledge and/or a sense of empowerment to take action? Yes, no, maybe and qualified, please.

DR. HABIG: Yes. Hardly any qualifiers. I think any information that a person with diabetes can get -- if they decide to go buy this test, already they are interested. And I don't see that further knowledge and empowerment is a detriment. So, simply, the answer is "yes."

DR. NIPPER: Thank you.

Ms. Rosenthal.

MS. ROSENTHAL: I think I will just say "yes."

DR. NIPPER: Thank you.

Dr. Harrington Falls.

DR. HARRINGTON FALLS: I will also say "yes." And I was also impressed in the presentation this morning that batch samples sometimes have decreased values and, therefore, an over-the-counter use could actually give us improved value.

DR. NIPPER: Dr. Clement.

DR. CLEMENT: My answer is also "yes," for the

reason that it may help wake up some of these patients that previously have been sort of sliding by and actually alert them that there is a problem.

DR. NIPPER: Dr. Boughman.

DR. BOUGHMAN: My answers actually would be to the three parts, "yes," "yes" and a qualifier on the word "action," the action that is expected from the patient as a result of the test is to call the health care professional. So, in fact, to take action themselves about their management directly as a result of the test, I think is calling it a little bit close. But Dr. Habig's comments about the added information and positive feedback, I think, are very important because any diabetic is going to have some problem at some time with their blood glucose levels and, in fact, I could see this in patients who are really trying to maintain self-management, that if they consistently had good results on a fructosamine test, in fact, they would have a -- that, in fact, would give them a sense of empowerment because, in fact, their overall control would be very good, even though there were an outlier here and there.

For those patients who are in extremely poor control or not monitoring themselves correctly, once again,

I am not sure that this would be a useful device or test.

DR. NIPPER: Dr. Rej.

DR. REJ: I would say "yes," but I would also qualify it by saying that it would not be diminished very much if you were to substitute for prescription use with over-the-counter use in that question.

DR. NIPPER: Thank you.

Dr. Goldsmith.

DR. GOLDSMITH: I would agree with Dr. Rej. Yes, but with the same qualifier.

DR. NIPPER: Thank you.

Dr. Cooper.

DR. COOPER: I agree with Dr. Rej.

DR. NIPPER: Thank you.

Dr. Zawadzki.

DR. ZAWADZKI: I agree with Dr. Rej and I would change the wording a little bit of the statement to agree with it and I would say just from the use of the meter and to take action with the help with the health care team.

I would also like to make a point, which was suggested by one of the other panel members. Most of the patients that we see actually take part in various health care plans that now more and more cover their diabetes

supplies. If we recommend something for over-the-counter use, that may not be covered by medical supplies that apply to prescription materials.

From that point of view, it might actually diminish interest in that use.

DR. NIPPER: Dr. Kurt.

DR. KURT: I agree with all of the previous things that have been said with the understanding that the prescriptive use would guarantee payment through a third party carrier and that should be weighed and how that reimbursement would occur with the approval process.

DR. NIPPER: I hesitate to correct any panel member or to censor any panel member, so, I hope this isn't interpreted that way. I think what we are talking here is safety and effectiveness and not reimbursement. So, I know that practical considerations do enter in, but I think we need to -- I would like to ask us to assume a perfect world and think about safety and effectiveness and predicate devices.

Dr. Rosenbloom.

DR. ROSENBLOOM: I agree with Dr. Rej's interpretation and opinion. The enhanced convenience, I am concerned, might be that it will be seen as a substitute for

blood glucose monitoring. If one looks at the responses of patients to questions about the device, about the system in here, it is very clear that patients do not have a clear understanding of the relationship between average blood glucose and the development of glycated serum proteins and that many of them just see it as another way of measuring blood glucose and would use it as, indeed, enhanced convenience, which means less blood sticks, will mean less blood sticks.

And for the other group that would be buying it, it would, indeed, enhance their sense of empowerment because that would be the group of people that have been addressed already, who are taking very good of their diabetes and want another measure of that success or another measure to modify their way of doing it. So, I think we are leaving out a large group, again, with the over-the-counter recommendation.

DR. NIPPER: Okay. Let's just -- keep the microphone and let's move to question 3 and think about harm to the patient as a result of misuse of information from this product as presented in the 510(k). What harm or what is the likelihood of harm to a patient as a result of inappropriate or misuse?

DR. ROSENBLOOM: Worst case scenario -- and I don't think I am the only one in the room who has experienced this -- a patient who is psychologically inappropriate for tight blood glucose monitoring sets goals which are dangerous, uses this device to achieve normal fructosamine levels as another measure, along with blood glucose monitoring, using a pump or multiple insulin injections and gets severe hypoglycemia, which is brain damaging or fatal. Worst case scenario.

DR. NIPPER: So, is that a "yes" or a "no" or a "maybe"?

DR. ROSENBLOOM: A possibility. It does occur. But that is true with self blood glucose monitoring as well. That can be done with self blood glucose monitoring, but this is another tool that could be inappropriately used without adequate supervision in that manner.

DR. NIPPER: Dr. Kurt.

DR. KURT: Yes, with the worst case scenario as described by Dr. Rosenbloom.

DR. NIPPER: Dr. Zawadzki.

DR. ZAWADZKI: There is a possibility, yes. I don't think it is likely in most settings, though.

DR. NIPPER: Do all three of you agree that the

likelihood that you are talking about, this worst case, is highly unlikely?

Dr. Rosenbloom, the worst case is highly unlikely or is it likely?

DR. ROSENBLOOM: Fortunately, it is not likely, but it can occur.

DR. NIPPER: So, there is a likelihood, but it is very remote.

DR. ROSENBLOOM: But it could even occur in a prescription setting. The patient gets the device in a prescriptive setting and then doesn't return for follow-up.

DR. NIPPER: So, it is not limited to non-prescription. It is limited to just --

DR. ROSENBLOOM: There may be a slightly greater likelihood in the non-prescription setting, I would say, or somewhat greater likelihood.

DR. NIPPER: Dr. Cooper.

DR. COOPER: Yes, I think you phrased it correctly. There is a likelihood and what we are discussing now is what is the degree of likelihood. To me, it is analogous to drugs that can be used. In some countries, you can purchase prescription drugs that are prescription drugs in this country over the counter and we don't generally do

this in this country because there is some likelihood of harm to patients.

So, I would say -- you are asking us to quantitate that and I would say that it is -- there is some likelihood. I would say that it is more than rare.

DR. NIPPER: Barbara.

DR. GOLDSMITH: I would agree with those comments. I mean, always there is the likelihood of harm if a patient chooses to act without consulting a physician and it sounds as though this would be in -- that this likelihood would occur in this extreme situation.

DR. NIPPER: Thank you.

Dr. Rej.

DR. REJ: I would say that the likelihood of harm as a result of potential misuse of information in the non-prescription setting and prescription setting or even in the laboratory setting is possible. So, I think that that -- it is a possibility. I still have a concern that a patient might elect to do this test rather than the glucose test. That, I think, is, at least in my mind, a little bit more real than remote.

DR. BOUGHMAN: I would suggest that the addition of this device to the cadre of different tests available

would not increase the likelihood of harm to a patient beyond the information or availability of any other test out there, so that the information gleaned from this device itself would not add or detract from harm being done directly to the patients in a setting that might become dangerous.

I believe there is one more subtle difference, though, that we have not discussed and that is while the recommendation would be to do this test once a week or once every two weeks, there may be the assertive or highly involved patients who, in fact, would test much more frequently, thereby, confusing or potentially muddling the information over a long term period of time. But that would be a more subtle kind of situation and not directly dangerous to an individual patient, merely muddling.

DR. NIPPER: Dr. Clement.

DR. CLEMENT: I would agree with most of the panelists that the likelihood is rare that there is actually harm. One issue that I think has not been brought up and has to do with the technique of the blood application to the device itself is that there is a potential -- again, this is a potential of harm. I am not sure how realistic this would be, that if a patient does not get an adequate blood sample

on the strip, if the meter still gives them a reading and gives a false, quote, unquote, normal reading, such as the reading is 300 and their actual overall glycemic control is very high, that could potentially do harm and give the patient a sense of complacency, where, in fact, their blood sugars really are higher than they should be.

Again, obviously, that information should be available through their own home glucose testing, but if the person is not doing home glucose testing and only buys this machine right off the shelf, without previous education and not doing home glucose testing, that is potentially a problem.

DR. HARRINGTON FALLS: Dr. Beverly Harrington Falls.

Considering the niche that this test overall has, it is not going to replace glucose monitoring. I can see some potential use just for glucose monitoring continuing to be over the counter because the last statistics I heard were 50 percent of people who were diabetic didn't even realize it and at least that way potentially people could be identified and know to seek health care.

As I mentioned in the morning session, early morning session, my concern was of people who without a

diagnosis of diabetes wanted to utilize the test and not having an understanding of what the appropriate place of the test was. I was impressed with the controls that have already been put into place by the manufacturer, including the batching of lots, the test strip, the control solution and so forth.

I appreciate the other panelists' remarks regarding the rare potential harm of a patient that was trying to remain in too tight of control.

DR. NIPPER: Thank you.

Ms. Rosenthal.

DR. ROSENBLOOM: I think it is a very rare potential harm. I think the patient that would react to that would have more quickly reacted to their daily blood glucose monitoring. So, I don't really see this as a consideration.

DR. NIPPER: Dr. Habig.

DR. HABIG: I think there is less likely harm to a patient as a result of this information than a patient who is monitoring their glucose. People monitoring their glucose might, in fact, take action based on an individual glucose result. This is, you know, an integration of glucose values over two weeks. The labeling is pretty clear

that it is not a substitute for glucose and that if the numbers are not in the expected range, to call a health care professional. I think the likelihood is low and in the event that the information is misused, I think the kind of -- amount of harm is also not great.

DR. NIPPER: Thank you.

I concur with Dr. Habig.

Question 4, is the performance of this device in the hands of the lay user appropriate to consider the device substantially equivalent; that is, as safe and effective as the predicate device?

So, Bob, when you answer this, we are talking about equivalence and that means equivalence in analytical technique as well as safety and effective.

Are other studies or other analyses of existing data also needed to define performance? So, we have folded two questions into one bracket here. So, I guess we will need two answers.

DR. HABIG: My answer to the first part of the question is "yes," I think the performance shows that it is substantially equivalent and is as safe and effective as the predicate device. But I do have some or a recommendation on the second part of the question.

In the 510(k) submission on the professional use or lab use LXN device, at least once, maybe twice the FDA asked for an analysis of the standard error of the estimate, which is, you know, how much scatter is there about the line and the data was not produced. Several different answers were given.

I would recommend that that data be produced before the determination by FDA is made so that you can really understand what the scatter about the line means.

Thank you.

DR. NIPPER: Thank you.

Ms. Rosenthal.

MS. ROSENTHAL: I think that the data shows that it is substantially equivalent and as safe and effective in the hands of the lay user as the professional.

Can you repeat the second question?

DR. NIPPER: Yes. Are other studies or other analyses of existing data also needed to define performance?

MS. ROSENTHAL: Well, I understand the concern about the scatter and the regression line, but I think the question then would be is it material. So, I really don't know what the answer to that would be for me.

DR. NIPPER: Okay. Thank you.

Dr. Harrington Falls.

DR. HARRINGTON FALLS: My main concern regarding this question is I do think it is safe and effective as the predicate device. Managed care has so tailored the use of the delivery system of health care now that I just am excited about being able to allow patients to have this available, prescription or otherwise. I think it would just give us more information and help with care.

DR. NIPPER: Thank you.

Do you think other studies are needed?

DR. HARRINGTON FALLS: I believe they can be -- the data can be compiled with use.

DR. NIPPER: Dr. Clement.

DR. CLEMENT: Yes. Steve Clement.

The answer to the first question is "yes." I think it is substantially equivalent.

As far as new studies, I would say for actually for this committee for marketing, I would say "no."

However, I would like to see a postmarketing study on efficacy of use of this device in one group of patients versus ones not using this device as an enhancement of SMBG and their long term outcomes.

DR. BOUGHMAN: Joann Boughman.

The performance of the device should be substantially equivalent since it is the same device as the predicate device in the laboratory. I would hope that it would be.

The other studies or analyses of existing data needed to determine the performance of the device, I concur with Dr. Clement that for the device, the answer would be for 510(k), no. However, are other studies or analyses of data needed to define the performance of patients with this device, yes, I think that a postmarketing study would give us additional information on patient performance and use of the device, not necessarily the device and its equivalents itself.

DR. NIPPER: Thank you.

Dr. Rej.

DR. REJ: I agree, again, since it is exactly the same device, one would expect it to be the same, although the skill of the operator might be a concern, but if an individual were to purchase this device either by prescription or over the counter, certainly their skills will improve with time. I don't think that is a major concern.

I am a little bit concerned with the data that was

presented by the sponsor, that did show this very wide scatter that just didn't jive with the coefficients of variation. I am not sure any laboratory studies are needed to resolve that, but perhaps an enhanced statistical analysis might be warranted.

And I think the postmarketing data would be useful to everyone.

DR. NIPPER: Bob, before you put the mike back, a follow-up question to that was that that data that you were concerned about with the scatter was first time use data. So, are you asking that we see the same kind of study after trained users are --

DR. REJ: If that postmarketing data were available, that would very quickly resolve that.

DR. NIPPER: Thank you.

Dr. Goldsmith.

DR. GOLDSMITH: My answer to the first question would be "yes" and I agree with the suggestion of a postmarketing study in follow up.

DR. NIPPER: Okay. Dr. Cooper.

DR. COOPER: I generally agree. I think that it is as safe and effective as the predicate device if it is used in the same manner as the predicate device, which I

understand is ordered by health care providers. And I don't see the need for additional studies.

DR. NIPPER: Okay. The question says in the hands of the lay user, though, is it substantially equivalent.

DR. COOPER: Yes, and it is a matter of interpretation. I interpret that "in the hands of the lay user" meaning in the home where the lay user extract the blood, obtains the sample and puts it into the machine. And I think under those circumstances, that part is technically correct. In terms of safety, however, the predicate machine is used in a slightly different circumstance and that was my point.

DR. NIPPER: Dr. Zawadzki.

DR. ZAWADZKI: I agree with the first question. I think the further market -- postmarketing data would be useful to answer the first question we have struggled with so much.

DR. NIPPER: Okay. Thank you.

DR. Kurt.

DR. KURT: I agree that the device apparently -it looks like it is, indeed, equivalent, the same device. I
think that the other studies, as suggested by Dr. Habig, in
other words, coming forth with the actual standard error of

equivalents and -- it must have been done, but is simply not supplied -- should be looked at.

I think that kind of a case for postmarketing, obviously, would be valuable and I have a question that arose after the manufacturer presented that I would be interested in the postmarketing portion in that I wonder if skin contamination by any substances, such as skin creams that might contain triethanolamine, because that is an amine, or using the insect repellent DET(?), which is diethyltoluramide(?), which is inoculated amine, would in some way -- if contaminating the blood specimen would interfere would interfere with the test.

DR. NIPPER: If any of the manufacturer's representatives know the answer to that question, please approach the podium and answer.

DR. BURD: Yes. John Burd.

We specifically did not test those substances, although, again, in our labeling relative to how the finger prick is supposed to be done, it tells the patient to make sure the surface of their finger is clean, but we certainly could perform those studies to see if there was a potential interference. But we have not done that.

DR. ROSENBLOOM: That raises the question of

alcohol. We are constantly telling people they don't need to use alcohol, but there is that psychological requirement to clean their finger with alcohol and if they don't wipe it off or let it dry well, they can get problems with blood glucose monitoring.

Have you looked at that issue?

DR. BURD: Not specifically with alcohol, but, again, we could test that.

DR. NIPPER: Thank you.

Dr. Rosenbloom.

DR. ROSENBLOOM: Yes, I agree with the substantial equivalence issue and -- but also I think one does have to look at both the possibility of improved performance and deteriorating performance of the test over time as people become more skilled. I am concerned about the training that would be involved. That is another reason to want this in the prescriptive manner so that people bring the machine to the -- usually the nurse clinician to learn how to use it properly.

DR. NIPPER: Okay. Are there other studies needed, do you think, Dr. Rosenbloom?

DR. ROSENBLOOM: Yes. As I said, I think that seeing what -- how performance occurs after a month or two

months or six months would be important data to have.

Unfortunately, we don't have that kind of data with blood glucose monitoring, but we know that patients make a lot of mistakes if they are not -- if they don't bring their meter in, have the meter checked, have their technique checked at regular intervals.

DR. NIPPER: Okay.

Let me ask a devil's advocate question since you brought up the problems of self-monitoring blood glucose. Since that is available over the counter and patients come and bring them to the doctor or the nurse to help with the technique issues and so forth, do you and the other physicians around the panel think that the same thing is likely if this device is over the counter?

DR. ROSENBLOOM: What same thing?

DR. NIPPER: That if they had problems they would bring it to you to get it fixed or to get instruction or to get help. In other words, would this be a natural flow for resolution of problem issues?

DR. ROSENBLOOM: Well, they will call and in most cases we will tell them if it is a technical problem, we will tell them to use the 1-800 number for the manufacturer and there is an excellent network and they will send out a

new machine by Federal Express and they send back the old one and so on or pick one up at the pharmacy. But that is a well-developed, well-informed physician, nurse population with that system. It would be a long time before there is that familiarity with this kind of thing.

So, I think the value, again, of the prescriptive requirement would be that it would be educating the health profession --

DR. NIPPER: The physicians.

DR. ROSENBLOOM: Well, physicians and nurses. I think in most of our settings, the nurses are doing all of this. It would be educating the health providers at the same time as it is educating the patients. So, I would think that would be an advantage from the manufacturer's standpoint in promoting the device and its application, but that postmarketing information would be extremely valuable to maintain the quality of the data.

DR. NIPPER: Do any other physicians around -- or any other panelists want to address that question? In other words, we have got an analogy that he brought up to self-monitoring blood glucose, which is over the counter. Would the same thing happen with this particular device?

DR. CLEMENT: I think that is a good analogy. And

there are going to be troubleshooting issues with this device I am sure, either anticipated or not anticipated by the company, but as far as how much harm can be done, I think that same analogy can be placed that the potential for harm is actually less in a glucose meter.

So, from the point of situation of whether it should be prescription or non-prescription, from that -- answering that question, I would answer that the OTC is probably okay.

DR. NIPPER: Thanks.

Dr. Rosenbloom, I would like to come back to you for question 5. Is the use of the device in the over-the-counter setting substantially equivalent; that is, as safe and effective as the use of the device in the prescription setting? So now we are getting down to the nitty gritty. Is your advice to the FDA over the counter or prescription setting? And if the answer is "yes," then you think it is substantially equivalent over the counter as to the predicate device in the prescription setting.

DR. ROSENBLOOM: Okay. Well, that gives me the opportunity to qualify my earlier comment about safety and the worst case scenario. As I mentioned, that worst case scenario can occur without this device or over the counter

or prescriptive. This just might be a contributor to that worst case rather than a direct cause thereof.

I would say as safe, probably. As effective, no.

DR. NIPPER: Dr. Kurt. Try safe and effective together.

[Laughter.]

DR. KURT: Safe and effective together, I think that an educational program with the physician's office, whether it is a prescription item or not, would be essential from the standpoint of it being truly effective. But from the standpoint of being really a risk to the life and limb of the patient would be extremely rare in the worst case scenario.

DR. NIPPER: Okay. I am not trying to gloss over the safety issues or the effectiveness issues, but when the FDA decides on clearance, they can't clear it as safe and not clear as effective.

DR. ROSENBLOOM: If it is "yes" and "no," it is "no."

DR. NIPPER: Okay.

DR. ZAWADZKI: I agree with Dr. Kurt that really the main issue here is the education of the individual consumer, as well as the individual -- the education of the

health care team in the use and the application of this kind of device.

There have been a lot of comments that the data we saw were for individuals, who are using the needle for the first time. When I think about this meter, though, using it every two to three weeks, as is implied by the actual physiology, it is really a first time use each time. So, I think that is probably the best data that one would get.

One wouldn't get better data with repeated use.

DR. NIPPER: Dr. Cooper.

DR. COOPER: Safe and effective, I would have to answer "no." I was going to comment earlier about the -- there are a lot of comparisons about this machine and the home glucose monitor, but I wasn't -- didn't participate in those decisions, of course, but I believe at the time that the glucose monitors were approved for in home use, both patients as a group and providers as a group had years and years of experience of interpreting what the glucose values meant. I am just afraid that fructosamine, there is not that that institutional knowledge of how to interpret the values and what you should do about it.

That is why I think that safe and effective over the counter, no.

DR. NIPPER: Okay.

Dr. Goldsmith.

DR. GOLDSMITH: I would agree with that. I would say "no." I think the prescription setting is safer, provided the prescriber is knowledgeable in the use of these results as stated earlier.

DR. NIPPER: Thank you.

Dr. Rej.

DR. REJ: I would say the efficacy of the device would be enhanced in a prescriptive setting. So, the answer would be "no."

DR. NIPPER: Thank you.

DR. BOUGHMAN: Joann Boughman.

I would concur.

DR. CLEMENT: Steve Clement.

I will be the devil's advocate and bring up the whole issue then -- in this situation with this device, I really don't think there is a big difference between over the counter and prescription because the physicians are going to be as illiterate or dumb about using this device as the patients and perhaps they should learn together. So, I would say it is a non-issue between OTC and prescription.

DR. NIPPER: So, the answer is "yes."

DR. CLEMENT: Yes.

DR. NIPPER: Okay. Thank you.

Dr. Harrington Falls.

DR. HARRINGTON FALLS: The question to me becomes whose responsibility is it to educate the health care providers. Should we do it ourselves or do the patients have to push us? Should the manufacturer come out and tell us all how it is supposed to be used? Or is the media going to say this is the new thing? And it will be out in the women's magazines and then we find out, oh, this is what everybody is expecting.

The developer did a very good job earlier this morning answering Dr. Rosenbloom's questions about the shelf life, making arrangements for that, making sure the strips cannot be adulterated and trying to standardize the process by using a pipele(?). So, I do believe that it would be substantially equivalent.

DR. NIPPER: Thank you.

Ms. Rosenthal.

DR. ROSENBLOOM: I would like to see it as a prescriptive device. I am concerned about somebody walking into a pharmacy and, frankly, being confused about which device they are purchasing and then it would fall to the

pharmacist to explain it to them, who I would think would maybe be less educated even than the physician.

So, I would like to see it as a prescriptive device.

DR. NIPPER: So, your answer is "no."

MS. ROSENTHAL: No.

DR. NIPPER: Dr. Habig.

DR. HABIG: I think -- my answer is "yes." I think that over the counter or prescription is not really going to change the safety and efficacy. I think it would be as equivalently safe and effective OTC as compared to prescription.

DR. NIPPER: Thank you.

I kind of skipped my answer to question 4. I could fake it and say I did it on purpose, but I forgot.

But they kind of roll in together. My opinion about this device as over the counter versus prescription, I must confess I am ambivalent. I remember a few years ago when I went to an ADCC symposium and heard about the benefits of tight control, self-monitoring, having a little bit of anxiety over loss of business and worrying over whether glucose monitoring could be done as effectively or as accurately as we could do it in the lab and seeing those

fears being dispelled by the benefits of tighter control.

So, in trying to determine whether or not I am willing to let go of my proprietary ownership of fructosamine as a power test as opposed to their test, I am willing to take the lead and see how well glucose self-monitoring seems to work and with the warts that we know that are there, I am willing to let it go over the counter.

But that is one voice and I am not voting. I am just telling you what I think.

We are going to move to a modified question 6. Do you have it on transparency?

Dr. Rej, did you want to say something?

DR. REJ: Yes. A little bit of a clarification regarding this over the counter and prescription use. I have a question for the FDA, perhaps Dr. Gutman. What would prevent me as an individual from just going out and buying this device today for my own home use? Even though the sponsor is not marketing as such, if there is something that is approved by the FDA or if someone is wealthy enough to buy a multi-channel analogue and have it in their basement --

DR. GUTMAN: I would guess that if you were really interested and tried to buy it, you probably could buy it.

You could misrepresent yourself as a professional even if you weren't, but the company certainly can't market it in that venue. They can't contract with Wal-Mart or K-Mart or Woolworth's and offer it.

DR. GUTMAN: If you try hard enough, I imagine, you know, going, beating down the door of any company and buying your own analyzer for your own basement, I guess that

DR. REJ: But an individual who really wants --

is possible. We don't police it quite that far.

DR. NIPPER: Your local illicit drug dealer will probably sell it.

So, did we have the modification of the last question? So, the question as stated in the handout is slightly different. Here is the question that is stated in the handout. If the product is considered equivalent, do you have any suggestions for enhancing the labeling? So, that is still there.

Then the FDA has asked us for additional information. In particular, we recognize differences in the way quality control is intended for OTC products versus the same product in professional use. We would appreciate input from the company and the panel on these differences.

So, let me ask the panel to tell us about labeling

suggestions and suggestions about changes in the way quality control is done on the product and then if there are not questions for the company, we will bring the company up to talk about quality control as well.

I will start with you, Bob. Dr. Habig.

DR. HABIG: I think for enhancing product labeling, it would be important to have clear -- "warning" sounds like a pretty strong term, but bold face type indication that this test is not a substitute for self-monitoring blood glucose testing, that it is to contribute to overall diabetes care by used complementary with self-monitoring of blood glucose testing.

I think that is my only recommendation.

DR. NIPPER: Okay. Do you have any concerns about the differences in QC?

DR. HABIG: I am going to say "no" because I don't actually have it in front of me to remember the specific details. I remember the control strip and solution to be applied. I actually don't even remember --

DR. NIPPER: Dr. Burd, why don't you tell us about the QC.

DR. BURD: John Burd.

Yes, we spoke about the quality control testing in

our presentation. Basically, the meter itself has a control strip, which allows you to know that the meter if performing properly and we do provide a liquid control solution with a defined value that the patient can use to assure that their test strips are working properly. So, if there is ever a question or a problem, they can use the meter and the test strip together with the control solution to see that the meter gives the proper result.

DR. NIPPER: How is the range of acceptable performance stated in the material? Because I didn't see that in the submission. Maybe I missed it.

DR. BURD: Again, it is very similar the predicate devices, the blood glucose testing devices, as well as the laboratory fructosamine devices. So, the ranges on the controls will be very similar to the ranges that you see with current blood glucose testing products for glucose, as well as the laboratory fructosamine.

DR. NIPPER: About how wide a target are you giving them to shoot at?

DR. BURD: For example, if the value is 250 micromolar, it would be somewhere between 220 and 280, that sort or range.

DR. NIPPER: Is that three standard deviations or

two?

DR. BURD: That would be, I believe, three standard deviations.

DR. NIPPER: Okay.

Does that help you, Bob?

DR. HABIG: Yes, it does.

DR. NIPPER: Now do you have an opinion?

DR. HABIG: I have a question first before the opinion.

Do you recommend in the labeling a frequency of testing with the quality control?

DR. BURD: Actually, Vivianne, would you like to respond to that?

Actually, while we are waiting for Vivianne, is it possible that I could respond to the earlier discussions about the safety and effectiveness? I will be happy to do that after this.

DR. NIPPER: Yes, we will ask you after we have gone around with this last question.

MS. NOETZEL: This is Vivianne Noetzel.

The control solution we recommend that you use it before you use the meter for the first time, at least once a month, when you begin a new bottle of test strips, whenever

you want to test that your meter and test strips are working properly, after cleaning your meter, if you drop your meter or on the advice of your doctor or health care professional.

DR. NIPPER: And if you replace the battery.

MS. NOETZEL: That is correct. In the battery section. That is correct.

DR. NIPPER: That wasn't in the list of when to use the controls, but it is in the list of -- when you replace the batteries, it tells you to rerun the controls, if I remember right.

MS. NOETZEL: That is correct.

DR. HABIG: Okay. Thank you for all that information and I have no recommendations for changing those.

DR. NIPPER: Now, we know why there are six strips in a bottle when you only test every couple of weeks.

Ms. Rosenthal.

MS. ROSENTHAL: I agree with Bob that I think it needs to be in bold print on it that it should not replace glucose monitoring.

I have a question. I don't remember any place in the labeling if you addressed complete cover with the blood of the strip or of the area of the strip that bleeds and I

wonder if there is not complete cover, what would happen.

DR. NIPPER: Is that a question for the company?

MS. ROSENTHAL: Yes. Yes, it is.

DR. NIPPER: Whoever would like to respond for the company is welcome to do so.

DR. BURD: John Burd. The question is what happens if there is not enough blood to cover the strip?

MS. ROSENTHAL: The area on the strip that is --

DR. BURD: Yes. Basically, again, the test strip has a molded part that has a little cup for application of the blood sample. We provide with the test what we call straws for collection, which have a little line on them, so that when you prick your finger and take the blood sample, blood will just flow into this straw up to the line. You touch the straw to the cup and it automatically dispenses that into the device. So, using the straw, there is no chance of them not getting enough blood into the test strip and if a user were not to use the test strip and were to put too small of an amount of blood on the sample, the software in the system, in the meter system, has indicators that too small of a sample has been added and you cannot put too much sample on the strip.

DR. NIPPER: Can you go back and add more and use

the same strip?

DR. BURD: No. That is not recommended and it cannot be done -- in the labeling would be the disclaimer for that.

DR. NIPPER: The labeling says not but the machine wouldn't know the difference, right?

DR. BURD: Possibly not. I mean, it may be again if you do that, that the kinetics of the reaction the meter sees might indicate that you are doing something improperly.

DR. NIPPER: So, it kind of monitors the reaction rate curve.

DR. BURD: Yes.

DR. NIPPER: Oh, that brings back old memories, doesn't it, Bob.

Okay. Thank you.

MS. ROSENTHAL: Well, then I think that the labeling is fine as it is and the quality control is fine also.

DR. NIPPER: Thank you very much.

Dr. Harrington Falls.

DR. HARRINGTON FALLS: To my earlier question, they had already referred me to page 13 regarding having a patient see a health care professional. I think, again,

warning about the use of the product if no diagnosis of diabetes has been given and not substituting it as an alternative for glucose testing alone and consideration of maybe listing that the 300 level is the upper normal might be worthwhile.

DR. NIPPER: Thank you.

Dr. Clement.

DR. CLEMENT: I agree with the previous comments about emphasizing not being a substitute for self-monitoring of blood glucose. I also noticed on page 16, where it has the labeling about what the different pictures of the strips on how much blood is okay, how much is not enough and how much is -- especially when there are lines on the back. I would emphasize or at least suggest that the sponsor put in bold labeling that if the quality control check that the patient does shows that there is not enough blood on the strip, that they should be warned that there could be a false result and that they should not use that result.

I understand there is some of that to prevent that from occurring, but in the rare case that it still may come up with a reading, which we often see with the reflectance meters we have available, I think that should be emphasized a little bit more.

DR. NIPPER: Thanks.

Dr. Boughman.

DR. BOUGHMAN: Thank you.

I would also not only suggest that -- in fact, hope that the FDA might require the labeling to include the warning about this not being a replacement for the self glucose monitoring. The sponsor has adequately answered the questions I had this morning. I would just reiterate a couple of small points, although I think they might be useful.

One is a reference to not needing fasting samples for this device versus the predicate device and to, in fact, reexamine the labeling regarding the cleaning of the machine to clarify a couple of potential problems there.

The enhancement of the labeling has been discussed in a couple of ways and I think would -- my only other suggestion would actually come back to the concept of whether this might end up as an OTC device or a prescriptive device, such that the normal ranges for non-diabetics and/or the nomogram that was shown earlier today might be appropriate for professionals to read and understand in detail. In fact, the lab professionals might well want to know what a normal non-diabetic range was.

However, if this is an over-the-counter device, including all of that information might, in fact, be more confusing than it is worth. So, the decision point would actually come before my final suggestions for enhancement or completeness of labeling.

DR. NIPPER: Dr. Rej.

DR. REJ: I think for the labeling, again, underscore the point that it is not a substitute for routine monitoring of glucose concentration. I don't know if I missed it, but I think that some disclaimer that there is no benefit for testing more frequently than on a bi-weekly basis might be there or whatever is decided.

I think the quality control regimen seems adequate to me.

DR. NIPPER: Thank you.

Dr. Goldsmith.

DR. GOLDSMITH: I would reiterate the concern I stated earlier not testing in certain patient populations, that they were not studied. Various members of the panel have referred patients with certain protein abnormalities, patients with nephrotic disease, pregnancy. I mentioned pediatric patients. You want to include in the labeling restricted use for certain patient populations.

I would encourage that some of these studies be done and perhaps if you restrict it to prescription, as we talked about earlier, that may, in fact, address this problem, but that would be my only concern.

I agree with the earlier comments of making sure that people know that this is not a substitute for routine blood glucose testing.

DR. NIPPER: Dr. Cooper.

DR. COOPER: Thank you.

I agree with all those comments. May I ask the company a question?

What is your feeling about low albumin? Is your decision that low albumin may or may not affect the results?

DR. BURD: Again, this is John Burd.

We rely heavily on -- Dr. Cefalu reported earlier that he actually had done quite a few studies with the laboratory fructosamine test and found that correction for albumin levels did not enhance the utility of the information. And there is a body of literature that talks about whether or not to use albumin corrections for fructosamine testing.

The consensus seems to be that it does not provide any enhancement and, in fact, can confuse things because you

are adding the imprecision of two measurements together if you try to utilize an albumin correction.

DR. COOPER: Okay. I see.

I am aware of the literature and the controversy and I didn't know what your position was on that. Thank you.

I agree with all of the comments, as I said. I wonder if some more limitations, such as it is not known the effect of acute illness on the -- I don't want this to sound like the interpretation of fructosamine but on the actual technical obtaining of that value because it is just not known. Acute phase reactives may interfere with the calorimetric test and we just don't know that. So, that would be a possible limitation that should be addressed, I think.

DR. NIPPER: Okay. That could also be additional studies that would be worth looking at.

Dr. Zawadzki.

DR. ZAWADZKI: In addition to the many suggestions so far, I think it would be helpful in the labeling to actually describe the vicissitudes of the glycemia that normally occur in the patient with diabetes and that the person who monitors blood glucose as 100 to 150 before meals

might actually have a fructosamine value that is high in the scale that was shown.

I think that scale would be helpful, but it is important to emphasize that fructosamine is an integrated value that we collect both pre-meal and post-meal glucose value and to just avoid perhaps some calls that might raise some concern among patients otherwise.

DR. NIPPER: Thank you.

Dr. Kurt.

DR. KURT: Yes. As stated by other panel members, I certainly don't think it is a substitute for blood glucose monitoring. I think that testing the system and some kind of an acute illness, such as the urinary tract infection that I suggested before would be helpful in knowing the reliability under those circumstances.

I think that it should be clear that the skin area that is being punctured should be washed clean so that it is not necessarily contaminated by some alkylated amine and that it be provided with some either audio or visual education program that is sold with the machine.

DR. NIPPER: Thank you.

Dr. Rosenbloom.

DR. ROSENBLOOM: Yes. I would recommend, as I did

earlier, that there be a separate packet or insert that is information for health professionals, so that when the device is purchased, either over the counter or by prescription, there is something that the patient can take to the health professional that may be beyond the eighth grade reading level and that can be -- and that would include a service number to call for further information or for reprints and so on, that there would be a very important educational component, as well as a training manual that the health professional could use in teaching patients how to use this.

In reference to pediatric and, I think, pregnant patients, although I will let Dr. Harrington Falls comment on that, I don't see an inherent reason why this device is not of value to those patient populations, in fact, is of greater value to those patient populations than stable Type II patients.

I think that it has its greatest value for those who have the greatest fluctuation in their blood glucose control from one week to the next. Therefore, I would simply emphasize that under no circumstances should this device be used or the values interpreted in pediatric or pregnant patients, except under close supervision of the

health provider.

DR. NIPPER: Thank you.

My opinion about enhancing the labeling was briefly alluded to by Dr. Kurt. I think that if the company doesn't already have plans to make a video tape of how to use the meter and the strips, how to take a good capillary sample and so forth, I think that would be very helpful. And these video tapes could be made a part of your detailed material to the physician community as well, so that instructing patients, the nurse could use the video tape appropriately.

I think that linking the patient that might want to use fructosamine to the physician through the back door not the front door is very helpful and I think when -- if the labeling emphasizes proper medical care of diabetics as a way to minimize sequelae and adverse effects of this horrible disease, I think that we could all benefit as a society.

I think that some of the panel's concerns about reimbursement -- I still remain an optimist that as the benefit of preventive measures and good tight monitoring becomes available to some of the newer modalities in medical care, that those benefits will encourage the community to --

those people to reimburse for preventive care, which is certainly an issue here.

I still remain concerned about misidentification of lots, in other words, using the wrong strip in the machine for a different lot. That is my only real concern. If the lot-to-lot differences between the strips are better than lot-to-lot differences between some glucose strips, then I am not as concerned. But I know that there are lot-to-lot differences in strips that can cause tremendous trouble.

So, I would like the company to take it as a professional responsibility to deal with that problem as appropriate with the FDA.

Quality control differences don't concern me too much as long as the range that the company provides is not too generous and doesn't allow problems to be overlooked.

That said, I think that I will stop at this point.

We have still a few minutes before we break for lunch and that would allow us to ask any questions of the company, to raise any other issues that are involved. Dr. Gutman would like to have the floor, so I will recognize him.

DR. GUTMAN: Since we have a little time and I

certainly want to allow the company also some time, but I just want to make sure that the quality control issue is clearly understood and perhaps you might conceptually think of it in terms of a broader wave of products that might reach the over-the-counter market in the future.

So, you might use this as a paradigm, but perhaps broaden, and that is that in the traditional laboratory setting, a product of this type has two controls run every time there is an assay. That is sort of a clear requirement the manufacturers have set towards that clear requirement. The technology may be racing ahead of the clear requirement and there is a lot of background discussion about how reasonable that clear requirement is, but right now that is a clear requirement.

The product as it is currently positioned is a little bit looser than that. It doesn't have a requirement for two quality controls to be run each time that the assay is to be positioned for use. Now, the history in glucose meters, and you will be getting a lot of opportunity to talk about glucose meters -- there is one where there has been a more liberal approach towards quality control. That may be great. That may not be so great.

The use of this product is a somewhat

supplementary type product, but I would still be very interested in having you in a sort of global context perhaps weigh in on the notion of not only the range, but also the frequency of testing. You may, in fact, feel that it is a very pragmatic alternative that the company has come up with here that is cost effective and that meets the needs of this test and that that ought to be, perhaps, looked at in a broader setting by FDA, as we are looking at products of this type or you might suggest that we look at it in some other way or that we, in fact, look at it in a more conservative way.

So, I would appreciate one more pass specifically looking at that issue of frequency.

DR. NIPPER: Okay.

Dr. Rej.

DR. REJ: That was a concern, but don't you think, Dr. Gutman, that the frequency of quality control in a home use situation would actually exceed that of a laboratory, In other words, the number of quality control tests to patient tests?

DR. GUTMAN: That would depend on how the product is labeled.

DR. REJ: From the labeling that I saw, to do it

every time, is at least one out of six, if they are a package of six. I think it was whenever you received -- opened a new bottle. So, that is already one out of six.

And I don't know how many laboratories -- what the frequency of quality control is, but I suspect for many tests it is much less than one in six, plus all the other -- then once a month. So, that is probably going to be two out of six and we are getting up to almost 50 percent of the strips being used for quality control.

Also, in addition, in the laboratory, a laboratory frequently encounters huge ranges in anilide concentration; whereas, with an individual patient, that is likely not to be the case. So, I share the concerns but I think, at least from my reading of this particular product, this seems appropriate.

DR. NIPPER: Dr. Boughman.

DR. BOUGHMAN: I also share those concerns, but I think Dr. Rej has, in fact, made the point and my opinion as a panel member would be that, in fact, in each case as the labeling and the device would come forward, that the question be phrased, in fact, as it was phrased here, for this device, for whatever device is being looked at, and its intended use, is the quality control sufficient. If that

question is asked distinctly enough, then the answer should be precise, accurate and cover those issues.

I would ask the company one more question in this context, however, and that is while Dr. Rej is correct that any single patient might not have the broad range from very low to very high, as we might see in a laboratory setting, in fact, if a reading is very high, for example, and then a week later the patient tests again without recalibrating to control that next time, what is the safeguard that, in fact, there might not have been a slippage from reading to reading? In other words, you read on a Thursday and it is very high. You read the next Thursday and do no quality control or cleaning in between. Is there — in the way the way the device works, is there a protection against that first high reading not affecting a reading the next time to make it falsely high?

DR. BURD: This is John Burd. And I am sad to say I don't quite understand your question.

DR. BOUGHMAN: In the recalibration of the machine from test to test, if a quality control strip is not used or the solution is not used to -- with a relatively normal measure before the test measure the second time, is there any reason to believe that a subsequent measure to a high

measure would read falsely high?

DR. REJ: I think the question has to do with maybe carryover. Is that right?

DR. BOUGHMAN: Yes.

DR. BURD: Each test is an independent event. So, there would be no carryover from the earlier result.

DR. BOUGHMAN: Okay.

DR. BURD: I hope that answers the question.

DR. NIPPER: Does anyone on the panel wish to add additional comments to Dr. Gutman's request?

Dr. Habig.

DR. HABIG: I think it is important for the FDA as reviewers to look at these new over-the-counter devices, to ask the submitters, the sponsors, to provide some confidence that the quality control scheme they recommend, in fact, provides adequate protection against deficiencies or errors or the kinds of things that can happen to the system.

At the same time, I would ask the FDA to remember technology is being enhanced and improved and the old paradigm of you have to do two levels of control every 24 hours is simply not adequate or is overkill for much of the technology that you guys will see as reviewers in the next several years.

DR. NIPPER: Any other comments?
[There was no response.]

The manufacturer asked for time to respond to the safety and effectiveness. Do you think we can do it in less than five minutes?

DR. BURD: John Burd.

Much less. Basically, I would -- just to wrap things up, I would like to -- to the panel, thank you all for your thoughtful consideration of our application. I think really it has been very thoughtful and a lot of good observations you have given to us.

We are very aware of the training and educational needs that our product is going to require and we have plans to put those educational and training articles in place.

I guess relative to the OTC versus the prescription use of the product, I would just like to restate what Dr. Harrington Falls pointed out, which is one of the current concerns I guess we have is that the possibility that uninformed health care professionals may stay uninformed if patients don't bring this to their attention.

But, again, I would like to say that we really appreciate all of your comments and we will certainly look

forward to working with the FDA on finalizing our application.

Thank you.

DR. NIPPER: Thank you for your words.

We are approaching the end of this session, the morning session. We are going to break for lunch momentarily and we will reconvene at 1 o'clock for an open public session. As nearly promptly as we can reconvene at 1:00 will be appreciated because we have a long agenda for the afternoon and the FDA won't let us up for air until 6:00 if we are not careful.

So, we are going to try to watch the clock closely this afternoon and we will look forward to a postprandial encounter with Dr. Gutman. So, with that, unless there is further business at this time, we will adjourn for lunch.

MS. LAPPALAINEN: Yes. I would like to say just one thing.

DR. NIPPER: The FDA always wants the last word.

MS. LAPPALAINEN: I would like to take this opportunity to thank the LXN Corporation for their fine presentation. I would like to thank the FDA and the reviewers in their hard work that they put together during the review of this. Of course, the review is not over.

I would also like to thank the panel for their very important and insightful input. I think was a great session and I would like to thank all of you for your participation.

And we look forward to this afternoon.

[Whereupon, at 12:00 noon, the meeting was recessed, to reconvene at 1:05 p.m., the same day, March 20, 1997.]

$\underline{A} \underline{F} \underline{T} \underline{E} \underline{R} \underline{N} \underline{O} \underline{O} \underline{N} \underline{S} \underline{E} \underline{S} \underline{S} \underline{I} \underline{O} \underline{N}$ [1:05 p.m.]

DR. NIPPER: Welcome to the afternoon session. It is entitled "Issues Regarding Self-Monitoring Blood Glucose Systems," or SMBG.

Before Dr. Alpert's prepared remarks -- okay. I have got a whisper in my ear that we are going to make you wait just a second until Sharon has a prepared comment and then we will go ahead.

MS. LAPPALAINEN: Yes. Good afternoon.

For the benefit of those of you who were not here this morning, I will reread my discussion from earlier this morning.

Good afternoon. I am Sharon Lappalainen, executive secretary of the Clinical Chemistry, Toxicology Devices Panel. We are here this afternoon to discuss the issues relating to self-monitoring of blood glucose.

I would like to acknowledge our former executive secretary, Ms. Cornelia Rooks. Ms. Rooks now pursues a new position as the director of the Division of User Programs and Systems Analysis. She has served with distinction as the executive secretary for the last five years and her service and dedication are to be commended. She will be sorely missed.

I would also like to introduce our new chairperson, Dr. Henry Nipper. Dr. Nipper is an associate professor of pathology at Creighton University in Omaha and he also serves as the dean of admissions to the medical school. He has made many insightful and valuable contributions during his past service to the panel.

Dr. Nipper replaces our former chairperson, Dr. Arthur Carmen, whose four year appointment was well served by both his characteristic style and sense of humor.

Welcome, Dr. Henry Nipper and welcome to our distinguished panel.

At this time, I would like each of the panel members to introduce themselves. Please state your name, affiliation and your current FDA panel advisory membership.

DR. NIPPER: So, we will start again with you, Dr. Rosenbloom.

DR. ROSENBLOOM: Arlen Rosenbloom, University of Florida, Gainesville. Temporary voting member.

DR. KURT: I am Dr. Tom Kurt, Dallas, UT

Southwestern Medical Center and I am a regular panel member.

DR. ZAWADZKI: Good afternoon. I am Joanna
Zawadzki. I am an endocrinologist in private practice in
the Rockville, Maryland area. I am a clinical associate

professor at Georgetown University Medical Center. I am a former member of Endocrine and Metabolic Advisory Committee.

DR. GUTMAN: I am Steve Gutman. I am the director of the Division of Clinical Laboratory Devices.

DR. COOPER: I am Jim Cooper. I am a senior medical advisor with the Agency for Health Care Policy and Research and I am on the faculty of the Uniformed Services University of Health Sciences.

DR. GOLDSMITH: I am Barbara Goldsmith. I am the associate director of the Department of Laboratory Medicine at St. Christopher's Hospital for Children, as well as the director of clinical chemistry there, and the associate professor in the Department of Pathology and Laboratory Medicine at MCP Hahnemann School of Medicine, Allegheny University of the Health Sciences.

DR. REJ: I am Robert Rej of the New York State

Department of Health with the State University of New York

at Albany. And I am a voting member of this panel.

DR. BOUGHMAN: Joann Boughman, regular member of the panel. I am currently vice president for academic affairs and dean of the graduate school at the University of Maryland, a geneticist by training and a professor in obstetrics, gynecology, epidemiology and preventive

medicine.

DR. CLEMENT: These titles are getting longer. I will try to keep it short.

Dr. Steve Clement, Georgetown University, a clinician, adult endocrinology and I am a temporary voting member.

DR. HARRINGTON FALLS: Beverly Harrington Falls, Cornerstone Health Care, private practice, OB-GYN, in High Point, North Carolina.

MS. ROSENTHAL: I am Ellen Rosenthal and my background is in engineering. I am the consumer rep to this committee.

DR. HABIG: I am Robert Habig. I am a director of corporate regulatory affairs at Bectin Dickinson and Company and I am the non-voting industry representative for the panel.

MS. LAPPALAINEN: For the record, I would like to read a conflict of interest statement for the Clinical Chemistry and Clinical Toxicology Devices Panel meeting,
March 20th and 21st, 1997.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an

impropriety. To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests.

However, the Agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government.

We would like to note for the record that none of the participants reported any involvements related to the fructosamine issue. A waiver has been granted for Ms. Ellen Rosenthal for her financial interest in a self-monitoring blood glucose or SMBG firm that could potentially be affected by the committee's deliberations.

The waiver permits this individual to participate in all matters before the panel. Copies of this waiver may be obtained from the Agency's Freedom of Information Office in Room 12A-25 of the Parklawn Building.

We would like to note for the record that the Agency took into consideration other matters regarding Drs.

Barbara Goldsmith and Henry Nipper. The financial interests

reported by these individuals are not related to the SMBG matters before the panel. Therefore, the Agency has determined that they may participate fully in the panel's deliberation.

We also note that Dr. Arlen Rosenbloom reported test strip studies with SMBG firms. However, since the studies ended more than ten years ago, the Agency has determined that he may participate in the panel's deliberation.

In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial interest, the participants should excuse themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Additionally, I would like to state that for the meeting today and tomorrow, Ms. Ellen Rosenthal will serve as consumer representative and Dr. Robert Habig will serve as the industry representative.

The following are our current members on the panel: Dr. Joann Boughman, Dr. Barbara Goldsmith, Dr. Robert Rej, Dr. Thomas Kurt and Dr. Beverly Harrington Falls. We also have the following temporary members to the panel: Dr. Steven Clement, Dr. James Cooper and Dr. Arlen Rosenbloom.

Thank you.

Now I will turn the panel over to Dr. Nipper.

Agenda Item: FDA Presentation -- Introduction to Self-Monitoring Blood Glucose Systems (SMBG)

DR. NIPPER: Okay. After that false start where I was trying to get Dr. Alpert on board a little early before the things that had to be said got said, I would like to welcome Dr. Susan Alpert. She is the director of the Office of Device Evaluation in the Center for Devices and Radiologic Health.

Welcome, Dr. Alpert.

DR. ALPERT: Thank you, Dr. Nipper, distinguished members of the panel and guests. First, I would like to thank all of you who are participating in the panel meeting today and tomorrow in advance for your time and effort on this very important issue.

What I would like to do in just a few minutes is,

if you will, set the stage for the discussions that will take place.

Diabetes is a very prevalent disease that affects millions of people in the U.S. and around the world. The ability of these patients to have more control over their health and a significant impact on their prognosis is critically important.

Home glucose monitoring has provided an avenue for such individual participation in disease management and has promoted better health for diabetics over the last three decades. During these same three decades we have learned more about the disease, better ways to manage glucose control and evolved ever-improving technologies which support glucose testing and insulin delivery by the affected individuals.

In addition, we have gained knowledge and experience regarding the impact of diabetes in both insulin dependent and non-insulin dependent patient populations. We can demonstrate in real terms less blindness, fewer patients with renal failure, the benefits of blood glucose control.

The technology currently available has already made a significant impact on the lives of the diabetic patient.

Earlier in our understanding of the disease, the medical community simply segregated diabetics into insulin dependent and non-insulin dependent categories and managed them differently. Today, as the medical literature indicates, there are many more recognized differences among patient groups that should also be included in the determination of individual patient management.

Examples of these considerations, which you probably know better even than I, include the number of doses and types of insulin used, if any, in a given patient, the pattern of a patient's disease, including their propensity for ketosis or hypoglycemia, the dietary control exercised by an individual, the exercise regimen of the patient and the ability of the patient to fully participate in their daily medical management.

In addition, the literature also reveals that diabetics are managed in many different ways, with many different goals. Some are managed with no blood or urine monitoring; some with daily urine monitoring alone; some with once-a-day blood testing and others with much more invasive testing and intensive testing regimens.

Even more recently, new blood and tissue glucose testing modalities have been in the news. Methods both more

and less invasive than finger stick blood testing are being evaluated for their potential benefits to the health and quality of life of diabetics around the world.

Given this growth of knowledge about the disease and the concurrent development of new technologies to monitor patients at home, it is appropriate that we assess their interface at this time. As we at FDA are challenged to evaluate new evolving technologies, we make benefits-to-risks assessment for each new product. These resulting decisions about the ability of new products to enter the marketplace and how we describe them in labeling to allow the user, be that health care practitioner or patient, to appropriately choose among available technologies in support of good health, have great impact.

We are looking for your assistance in this very important area in consideration of devices for home monitoring among individuals with diabetes. We seek your help in evaluating the bases upon which we should be making these benefits-to-risks ratios.

The areas that we will discuss range from appropriate patient identification to the reliability and performance of underlying tests to specific outcomes we should expect for common or new technologies. During the

first part of this panel session, we would like to focus on the potential needs of different populations of diabetic patients.

Later in the day and tomorrow we will focus on how we currently at FDA evaluate products in this area and seek your advice on how we might improve the way we do these assessments. We are here to learn. We are here together to develop approaches that allow us, where possible, to even anticipate the changing technologies and their impact on patient care.

By the end of these two days, we hope to better understand varying diabetic patients' needs in order to focus both product development and premarket review on meeting these needs. We want to focus on the types of assessments that should be the basis for our reviews, to assure that new devices entering the marketplace are safe and effective for their users.

Our goal is to continue with the medical device industry to provide products that improve the health of the diabetic patient, devices that address the real issues in disease management.

Once again, I would like to thank you in advance for your work with us on this very important public health

issue.

DR. NIPPER: Thank you very much, Dr. Alpert.

The next presentation will be by Dr. Steven

Gutman, who is the director of the Division of Clinical

Laboratory Devices, affectionately known as DCLD, Office of

Device Education, ODE, Center for Devices and Radiological

Health, CDRH. See, I have been required to learn these

abbreviations as part of this new job. But I am still doing

it with prompters.

Dr. Gutman, we appreciate your being here and we are looking forward to your presentation.

DR. GUTMAN: Thank you.

To perhaps expand the stage for the next day and a half, I will spend the next few minutes providing some brief background information.

I will review the evolution of glucose meter use, their clinical importance and FDA's involvement in the premarket review of self-monitoring blood glucose systems. Let me also express at the start that I appreciate the interest in this subject by everyone who is at today's meeting as a member of the panel, a speaker or member of the audience.

We are fortunate to have people here who represent

the different parties involved with the use of glucose meters, including the industry, health care professionals and consumers.

Glucose measurements play a pivotal role in both the diagnosis and management of diabetes. Refinements in testing have in large measure contributed to our increasing understanding of the biology of diabetes and its differing subgroups. Indeed, although the discovery of insulin and its therapeutic benefits is usually thought of as the sentinel event in the history of diabetes, the implementation of portable glucose testing at the bedside or at home clearly represents a parallel revolutionary breakthrough.

The availability of this technique to help refine diabetic therapy is the cornerstone of the diabetes control and complications trial. This study clearly defined both the benefits and the risks of tight control and clearly stands as a benchmark for ideal therapy in insulin dependent diabetes.

Many diabetic patients are, however, not insulin dependent and in many subgroups of patients with this disease, intensive therapy is not an appropriate management goal. Trying to assist in assuring the correct match

between the differing needs of varying patient subgroups and the diagnostic and therapeutic choices available to them is a continuous challenge to clinicians, manufacturers and even regulators.

In 1963, Ames, using modifications of his methodology for enzymatic measurement of glucose in urine, introduced the dextrose sticks, the first visual test strip for measuring glucose in capillary blood. Although preliminary reports nicely described both analytical and user limitations in this methodology, as early as 1965, an anecdotal report appeared in the medical literature on the use of the product at home by a patient with gestational diabetes.

The first report on a portable reflectance meter to standardize readout on this type of glucose test strip was published in 1970. Subsequent reports demonstrated that such a device could produce reproducible and accurate results with a high correlation to standard laboratory methods.

In 1978, two papers appeared in Lancet describing the benefits of home blood glucose testing. Sixty-four diabetic patients were studied at St. Thomas Hospital Medical School in London, England, using the Ames I-Tone(?)

Meter and 69 diabetic patients were studied at the General Hospital in Nottingham, England, using the Berringer Ringer Manheim Meter. The conclusions of these studies were similar. Use of home blood glucose monitor produced easier and more predictable glucose control with a reduced number of hypoglycemic episodes.

Although the pros and cons of home testing were matters of spirited discussion in the medical literature over the next few years, by 1982, the American Diabetes Association had clearly formulated goals for ideal management of diabetes. In a formal policy statement published in Diabetes Care, the ADA noted self-monitoring of blood glucose is, quote, preferable to urine testing in any insulin-requiring diabetic patient.

This recommendation was taken to heart in an explosive manner. Estimates suggest that by 1986, home blood glucose monitoring was practiced on a regular or intermittent basis by one million diabetics. By 1992, this estimated number had risen to over three million and current sales of blood glucose meters in strips are estimated to be over \$640 million a year.

Driven by a clear medical need, technological advances in a strong commercial market, glucose meters and

strips have undergone a complex series of innovative refinements. The meters have become smaller, faster and more user friendly. Expectations for improved performance have in large part been stimulated by these changes.

In 1986, a diabetic consensus conference proposed for the first time performance goals for glucose systems. As a starting recommendation, the assembled expert panel recommended that the goal of all future SMBG systems should be to achieve a variability of 10 percent at glucose concentrations of 30 to 400 -- that is an error in the slide -- of 30 to 400 milligrams per deciliter, 100 percent of the time.

Unfortunately, variability was not very well defined. In subsequent citations, this performance goal has been variously viewed as a precision goal, an accuracy goal or a goal for total system error considering the sum of both the precision and accuracy goals.

The 1986 panel also recommended that with current systems, SMBG measurement should be within 15 percent of the results of the reference measurements. It was suggested that matrix specificity be maintained in evaluating the glucose technique. However, definitions of what reference methods or predicates should be used for comparison testing,

how to do deal with choices of different matrices and whether the 15 percent match should be considered an evaluation of bias alone or a more complete measure of total error incorporating estimates of both systematic and random error components or all issues left somewhat unclear.

In 1992, the 1986 recommendations were revisited and tighter ideal diagnostic objectives were proposed. In a statement subsequently published in Diabetes Care in 1995, it was suggested that the goal of SMBG device manufacturers should be to make future SMBG systems with an analytical error of 5 percent. That is a very challenging goal.

FDA regulation of glucose meters, like that of most other devices, dates to the passage of the Medical Device Amendments of 1976. Our records indicate that the agency cleared its first home monitoring system in 1979. Since then, these systems have been one of the most commonly reviewed products for over-the-counter use. The Agency has cleared over a hundred SMBG systems.

The mechanism for review of these submissions has been through the premarket notification or so-called 510(k) process, one which you as a panel now are familiar with, having done a similar process this morning.

The most basic precept in review of these devices

is an evaluation of analytical performance in the hands of the intended user; in the case of home testing, lay users with diabetes. Demonstration of this performance tends to be comparative, preferably against a reference method, but practically most often against a well-defined and wellcharacterized laboratory predicate.

In addition to demonstration of performance in the hands of lay users, FDA asks for information directed at demonstrating the impact of hematocrits, altitudes, common analytical interferences and potential electromagnetic interferences on device performance.

FDA recommends its sponsors follow the labeling guidelines established by NCCLS, the National Committee for Clinical Laboratory Standards, in their document "Labeling of Home Use In Vitro Testing Products." And we also recommend that sponsors refer to available FDA guidance documents, such as "Write it Right" and "The Points to Consider Regarding Labeling and Premarket Submission for Home Use In Vitro Diagnostic Devices," to assist the sponsor in developing clear, coherent and user friendly language.

FDA review does not specifically require manufacturers to demonstrate the various components of method error according to source, but we do look at the

magnitude of that error in the course of the review and in considering a clearance decision.

Review of performance in the world of current 510(k) submissions suggests that reasonable performance goals are almost universally attainable. In eight submissions cleared by our division over the past year, for example, using 200 milligram per deciliter as an important medical decision point, total precision estimates range from a low of 5 to a high of 13 percent; total bias estimates from a low of less than 1 to a high of 12 percent and the total error combining these elements of systematic and random error were on average, 12 percent.

In spite of our efforts to define performance in terms which represent real world use, there is evidence to suggest that performance outside of FDA submissions falls short of the mark being reported in our submissions and in manufacturers' package inserts. In Q-Probe studies reported by the College of American Pathologists in 1993 and then again in 1996, as many as 26 percent of glucose readings failed to agree within 15 percent of the institutions' conventional laboratory method for glucose testing.

Now, this in part represents the fact that these studies may not have been matrix specific, probably were not

matrix specific, and occurred in various use settings.

Field testing by ECRI using accuracy goals of 15, 20 and 25

percent to establish a range of above average, average and

below average ratings have repeatedly suggested that some

tested devices could not be recommended for home use.

Finally, a number of literature reports have suggested that FDA review and manufacturers' performance claims sometimes fail to predict performance when challenged in the real world of testing. These inconsistencies in review data and testing outcomes are matters of obvious interest to the agency and we would like to consider mechanisms we might implement for improving the prediction of real world performance and ensuring that device labeling reflects a performance in a user-friendly manner.

Ms. Rooks will be presenting key elements of our existing guidance for home glucose monitors and suggesting some possible areas where we might strengthen our review process. In the course of this meeting and the weeks that follow, we are seeking broad public input on mechanisms for things we can do to improve the accuracy and reliability of these devices.

We are also interested in obtaining perspectives from manufacturers and from users of these devices to

determine the issues at play in the loss of performance and in determining ways that these can be addressed.

Finally, as Dr. Alpert suggested, the Agency appreciates that invasive technology is improving and that new non-invasive technologies are under development and evaluation. We are seeking input on performance goals and appropriate study designs, which might be used to help foster the rapid transfer of these improvements into the real world of testing.

We are hoping to use this panel input as a starting point for dialogue with both the professional and manufacturing communities in trying to contribute to continuous quality improvement of home glucose monitoring devices in their use and in building a public/private partnership that will improve outcomes in the management of patients with diabetes.

Anybody have any questions?
[There was no response.]

DR. NIPPER: Thank you very much, Dr. Gutman. I am sure we will have questions for you and the other FDA representatives during the course of this day and a half.

You have laid out a challenge for us that I hope we can meet.

At this point in the agenda we are about to open the floor for public -- for an open public session on perspectives on the current use of self-monitoring blood glucose devices. Speaking to the panel and to the audience today will be public attendees, who have contacted the executive secretary prior to the meeting and they will address the panel and present material and information relevant to the agenda before us.

We ask each speaker to state whether or not they have any financial involvement with manufacturers of any products being discussed or with their competitors.

As I am tapped to be "Father Time," I don't know whether we have a light device or not to say when the 15 minutes is up or not. I don't believe we do. I will try to flag you down if you run a little over the 15 minutes. If you have time to give back, I am sure that all of us will appreciate it because we have a full agenda for the day.

At this time, the first person on our list is Dr.

John W. Ross. Dr. Ross is here as a member of the College

of American Pathologists, which is located here in

Washington on I Street. I am turning the podium over to Dr.

Ross for 15 minutes.

Agenda Item: Open Public Session

DR. ROSS: Thank you. I am John Ross, a practicing pathologist at Kennestone Hospital in Marietta, Georgia. I have no financial interest in any of the self-monitoring blood glucose systems, glucose meters and test strips on the market or under development.

I am here today representing the College of American Pathologists, the CAP, where I serve as chair of the Chemistry Resource Committee. The College is a medical specialty society representing more than 15,000 physicians, board certified in either anatomic and/or clinical pathology. College members practice their specialty in community hospitals, independent clinical laboratories, academic medical centers and federal and state facilities.

Since its inception in 1947, the CAP has developed a laboratory standards and is considered a leader in the field of laboratory quality assurance programs.

I thank you for the opportunity to address the Clinical Chemistry and Clinical Toxicology Committee and I would like to frame my discussion today in the context of blood glucose monitoring devices used in the clinical inpatient setting.

My statement will address the following areas first; a discussion of the attributes and disadvantages of

alternate site testing; secondly, blood glucose monitoring devices as alternate site testing procedures and, third, a brief overview of the CAP's comments on the FDA draft and review criteria for review of blood glucose monitoring devices and their labeling.

With reference to alternate site testing, we feel that any discussion of the use of blood glucose monitor devices used in the clinical inpatient setting would not be complete without the discussing of the general alternate site testing technology.

For purposes of this discussion, alternate site testing, that is, AST, is defined as clinical laboratory activities that take place outside of the physical confines of the hospital's principal laboratory, but under administrative control of the hospital. The position of the CAP is to support and encourage the development of new technologies to facilitate the delivery of quality patient care services.

In this regard, the CAP recognizes that alternate site testing is an integral part of laboratory medicine.

Some of the benefits associated with AST are decreased turnaround time, small specimen volume and low specimen acquisition costs and the potential to lower central

laboratory fixed costs. Despite its advantages, issues, such as overall quality of testing results, potential duplication of equipment and inefficient use of personnel require careful and cautious implementation of AST programs.

High quality patient care should be first and foremost in the delivery of all health care services, including AST. For this reason, it is the CAP's position that certain basic principles must apply to AST.

First, AST must not introduce or augment clinically significant errors in the testing process.

Therefore, AST must meet the same standards as do all other clinical laboratory services, including adherence to good laboratory practice; that is, quality control, quality assurance, proficiency and recording of results in the patient's medical record.

Secondly, development of AST programs should actively involve all participants, including laboratory staff, nursing, medical staff, administration and other health care professionals.

Third, the technologic development of AST must be appropriately applied for maximum patient benefit. This will require active dialogue with health care manufacturers.

Fourthly, efforts must be made to quantify and

compare all costs and benefits associated with AST and other testing modalities. Bedside blood glucose monitoring is the oldest and most common AST procedure. However, controversy continues over the ability of this technology to provide precise and accurate testing results in the inpatient setting.

Under the regulations implementing the CLIA(?)
'88, blood glucose monitoring devices are generally lumped
into the Wade(?) Test category and as thus, are defined as
simple, accurate methodologies that make the likelihood of
error negligible or pose no risk of harm to the patient if
the test is reported incorrectly.

The CLIA regulations require only adherence to manufacturer recommendations as the quality control mechanism, the Wade Test procedures. The CAP believes that blood glucose monitoring performed as an AST procedure is more appropriately classified as a moderate complexity diagnostic procedure. Although the in vitro blood glucose monitoring device used in the invasion setting is similar to that used in the home setting, the test process as a whole differs in complexity from that seen in the ambulatory home testing environment.

I will offer the following examples of the

increased risk associated with blood glucose monitoring in the inpatient setting. The risk of patient or recorded identification error is increased due to providers in the AST setting, caring for multiple patients simultaneously and the fact that the operator performing the test in the AST setting is not necessarily the provider charting the test, assessing the test result and changing the medication on the basis of the test result.

The risk of poor sample quality is also increased due to the prevalence of poor peripheral circulation and conditions of circulatory collapse. Moreover, the risk of variation in operator skill is greater in the inpatient setting than in the home environment.

Therefore, it is the CAP's position that when performed as an AST procedure, it is inappropriate for laboratories or alternate site testing areas to rely solely on manufacturers for test reliability and blood glucose monitors. Instead, the CAP recommends that blood glucose monitoring conducted as an AST procedure adhere to quality assurance standards; that is, quality control, proficiency testing, patient test management, et cetera, in order to assure the delivery of quality health care services and ultimately to improve the patient outcomes.

The ability of blood glucose monitors used in AST settings to produce accurate results was evaluated in a 1994 CAP quality assurance study by 144 institutions, who submitted data for the study. The study results indicated that a higher degree of accuracy was achieved for blood glucose monitoring programs when several quality assurance mechanisms were incorporated into the AST program, including use of laboratory personnel as blood glucose monitor operators, repeated training and/or performance review at scheduled intervals for operators, regular comparison of blood glucose monitoring results with clinical laboratory results and use of the blood glucose monitor's capability to store OC results and/or patient data.

With regard to the review criteria draft document, the CAP believes that the FDA document should be revised to help improve intra-method comparison among manufacturers, process control in alternate site testing and correlation with established clinical standards.

Due to the technical nature of the CAP's comments on the FDA review criteria document and available time, I will not address the comments as a formal part of my presentation today and have submitted them by a separate letter. I will be happy to cover those in about another

four minutes, at the end of this statement, if you would like me to do so.

In conclusion, the CAP recognizes that blood glucose monitoring as an AST procedure is a valuable testing methodology for the care of diabetic patients. However, issues surrounding the ability of the technology to provide precise and accurate testing results in the inpatient setting must be resolved in order to improve patient outcomes.

Similar to all AST procedures, the CAP's position is that certain basic principles must apply to blood glucose monitoring in the inpatient setting, including adherence to standards of good laboratory practice in order to assure the delivery of quality health care services and to improve patient outcomes.

Dr. Nipper, I could cover a two page letter that is addressed to Dr. Joseph Hackett, with somewhat more technical recommendations if you would care to take that time.

DR. NIPPER: I believe you have the time. Go ahead. If you can do it in four minutes, that would be wonderful.

DR. ROSS: I think I can.

The letter addressed to Dr. Hackett begins with our appreciation for being invited and offered this opportunity.

The CAP believes that the review document could be revised to help improve, first, intramethod comparison among manufacturers; secondly, process control and alternate site testing and, third, correlation with established clinical standards.

Our comments below will address these three areas and we also enclosed some specific language revisions for the review criteria document.

With regard to intramethod comparison among manufacturers, data from the CAP surveys, that is, proficiency testing programs, suggest that some of the disagreement among blood glucose monitoring methods may be due to intramethod differences in calibration. This arises from three sources; first, variation in the selection of reference material; second, variation in selection of the reference method and, thirdly, variation in the calibration of the reference method that is selected.

Manufacturers' claims regarding whole blood, plasma, venous, capillary, et cetera, calibration are unclear and difficult to verify. For instance, a serum

plasma, hexokinase NRSCL credentialed reference method is available for glucose analysis. However, a credentialed reference method for whole blood glucose, such as is mentioned in Section 4(c) of the review criteria document, is not available.

The CAP believes that intramethod standardization will be enhanced by use of venous whole blood as the test sample and use of venous plasma as the reference material with correlation to the NRSCL credentialed reference method for plasma glucose for the following reasons:

Since clinical guidelines for glucose interpretation are established by use of venous plasma, correlation with established clinical guidelines will be enhanced by use of venous plasma as a preferred reference material. Furthermore, clinical plasma analyzers may be calibrated satisfactorily to the NRSCL credentialed reference method for glucose.

Properly calibrated clinical plasma analyzers using either glucose oxidase or hexokinase methods are acceptable. Glucose oxidase methods with direct electrode detection of hydrogen peroxide are probably superior when they are properly calibrated to plasma glucose values.

Venous blood, if used, may be oxygenated if

necessary. With regard to process control in the alternate site testing environment, regulations implementing the Clinical Laboratory Improvement Amendments of '88 to require only adherence to manufacturers' recommendations for process control of Wade Tests.

However, the relationship between institutional policy and the manufacturers' recommendation is not clearly defined. For example, a leading vendor's total quality management manual provides in a section entitled "Proficiency Testing," the following information. The proficiency test information stored in the electronic data storage module, blanks for entry of the type of personnel performing proficiency testing, including, quote, operator and, quote, other; a check off for an interval at which proficiency tests are performed, including 1, 3 and 4 months and, quote, other; a blank for the name of an external proficiency testing program.

However, a separate document provided by the same vendor entitled "Regulatory Summary," states that the vendor makes no recommendation regarding proficiency testing, either external or internal.

In the total quality management manual provided by this vendor, either options are listed for the control

sample interval. The options include, quote, other, quote, each time a new vial of test strips is opened and, quote, if the electronic data storage device has been dropped. The attached regulatory summary states that the vendor's recommendation is to perform control sample testing when each new vial of reagents is opened.

The regulatory summary sheet also states that the vendor has no recommendations regarding validation of method decision, method accuracy, calibration checks, periodic checks with the comparative method, that is, internal DT, reporting range or linearity.

Due to the dependence of regulatory agencies on manufacturer guidelines, the review criteria document should be revised to require clear and more specific manufacturer recommendations for quality assurance in the inpatient alternate site testing setting that assure a degree of process control appropriate to that setting.

I will mention only one other specific technical recommendation, which has to do with use of reference to the NCCLS document EP9, "Method Comparison and Bias Estimation Using Patient Samples," specifically in Section 4(d) of that review criteria document.

DR. NIPPER: I don't think that noise has anything

to do with your taking too long.

DR. ROSS: I think I can finish in 30 seconds.

Moreover, in the same section, 4(d), the appropriate formula for calculation of total errors should be provided by the manufacturer. At a minimum, the probability, which with the calculated total error limit holds and whether the limit is a 1 or 2 tailed distribution should be provided. A quadratic formula with a 95 percent probability that the correct result is in a two-tailed distribution is one appropriate model that may be used.

Dr. Nipper, that concludes my statement and I thank you for this opportunity.

DR. NIPPER: Thank you for presenting the technical details. I am sure they will help us in our deliberations.

The activity you saw up here, we were trying to follow a couple of sections in the guidance document. We found out we were missing a couple pages. So, we went to get the right ones.

DR. ROSS: I see.

DR. NIPPER: Thank you, Dr. Ross.

DR. ROSS: Thank you.

DR. NIPPER: The next individual who we will call

upon to present is Dr. Richard Kahn(?), representing the American Diabetes Association. They are headquartered on Duke Street in Alexandria, Virginia.

Dr. Kahn, you are --

MS. HENSEN: I spoke with Dr. Kahn night before last and he asked me to forward some comment on behalf of ADA.

DR. NIPPER: Okay.

Are you going to present?

MS. HENSEN: I had originally called to schedule to present on behalf of the American Association of Diabetes Educators, but would be glad to share comments from both organizations as I volunteer a lot with them.

DR. NIPPER: Are you Ms. Hensen?

MS. HENSEN: Yes, ma'am. Yes, sir.

DR. NIPPER: You are right to say "Yes, ma'am" to her.

I certainly have no objection to your going ahead today.

MS. HENSEN: Thank you, Dr. Nipper and panel members.

I have no financial interest in any of the monitoring companies. However, as with Dr. Rosenbloom, have

had the opportunity to be involved in testing of strips and meters in years past.

I appreciate the opportunity to address comments to this panel today as they relate to glucose monitoring.

As Dr. Alpert and Dr. Gutman have shared, there are millions of people with diabetes. And with the probable release of the new American Diabetes Association criteria for diagnosis, that would lower the level at which diabetes is diagnosed to a fasting plasma glucose of 125, clinicians are faced with advising potentially millions more of patients with diabetes.

Add to this, the enormous body of evidence that glycemic control prevents microvascular complication and the impetus for careful monitoring and managing diabetes is clearly felt by all clinicians.

The consequences of poor control are not just the devastating chronic complications, but the escalating costs associated with dialysis, heart disease, increased utilization of the health care system, days lost from work and so on.

The DCCT is the primary body of science, of course, that has driven the standards of care that have been put forth by ADA, which would in summary, of course, tell us

that the goal would be to have the fasting blood sugar at 80 to 120 and take action in changing the management plan if those goals are less than 80 or above 140 or if the hemoglobin A1C is greater than 8.

Monitoring this level of glycemic control requires accurate and user friendly methods of glucose management.

Self-monitoring of blood glucose is the standard and people with diabetes live with, monitor and in many cases self-adjust all parameters of their own diabetes regimen.

While clinicians use the hemoglobin A1C as their gold standard of longer term glycemic control, the devil is in the details. The daily glucose records provided by the patient supply the information by which insulin and oral agents are titrated, specific meal doses are adjusted and basal insulin dose decisions are made.

Blood glucose levels cannot accurately be determined by feelings or symptoms or by urine testing. It is necessary that we have glucose data. Any new systems, non-invasive, implantable or minimally invasive, must be accurate, precise and reproducible. They should be tested in the environment in which they will be used on sufficient numbers of Americans, representative of patients with diabetes that will be using them.

Achieving accuracy has been addressed by several of the previous speakers and I will defer to their comments and move on in the effort of saving time. But I do want to make a comment about who should test and that has been addressed by the ADA Consensus Conference of 1993 to not just include people that have insulin dependent diabetes or non-insulin dependent diabetes, but those that are considering conception and those that have gestational diabetes.

In terms of frequency of testing and what we are seeing clinicians recommend, certainly increased testing is suggested for patients with hypoglycemia unawareness, pregnancy, intensive insulin management, insulin pump therapy, sick day management and erratic lifestyles, such as those working swing shifts or traveling frequently.

Many clinicians are currently recommending the highest testing frequency for patients taking Life Pro insulin. Testing in this case is requested sometimes as often as fasting, one to two hour postprandial, pre-meal and bedtime. This allows, of course, titration of the Life Pro dose, as well as assessment of the basal insulin needs.

Additional pharmacotherapeutic agents have come on to the market in the last couple of years and they have also

changed the testing patterns and the frequency that we are seeing clinically recommended, not just Life Pro humologue(?), but Metformin(?), Acarbose(?) and Yontroglitizone(?), all will seem to be able to be titrated more effectively if postprandial blood glucose assessments are made, rather than pre-meal testing.

The levels of glucose control and the targets that are set for different groups is another area that was requested input from this group and the ADA guidelines, again, give us suggestions for that and that is supported by science from DCCT, the Kimomoto(?) study, the U.K. diabetes study and other than the very young, those under seven, or the elderly, as determined by level of complications, cognitive and dexterity problems, we would expect to target those goals that were previously mentioned.

There may be other groups that would have an adjustment in their glycemic goals. Those people with gastropuresis, hypoglycemia unawareness and other patients or clients that have hypoglycemia as a serious health consequence.

Even with these concerns, clinicians are not accepting previous norms of glucose values in the 200s. The overall clinical goal is to reduce the hemoglobin A1C, no

matter what the starting point. In lieu of non-invasive testing or an implantable closed loop system, the current monitoring technology while showing vast improvements still has some fallacies.

Errors in monitoring continue to be divided into several categories; user errors by both patients and health professionals, interferences from patient's conditions, medications and meter strips and limitations.

I would like to address initially some of the user errors that we see. And I would start with the problems related to control testing. We see that control testing is not done routinely. I had a patient this week come in with his meter, strips and all of the supplies and was proud that he had his control solution with him. It was dated 1992. So, we see that patients are not having control solution. They are not instructed. It is not up to date and they perceive doing control testing as a waste of one or two strips.

Health professionals perceive it as probably a waste of time, but Joint Commission and others certainly require that. And it is a help to have new systems in place that lock out, if you will, the ability to test until that QC is done. But I might make several suggestions in this

area.

All meter systems, it would help if they had built in the lock-out feature with overrides only in case of the need for emergency testing. Glucose control solutions could be universal for all meters. That would help greatly. The cost for control solutions should be drastically reduced.

Make them a service item, a loss leader, provide them with each can or package of test strips.

Massive pharmacist education should be undertaken to emphasize the importance of control solutions and the necessity of having it on the shelf. And massive pharmacist education should be undertaken to verify hands on competency with meters that are sold in the retail settings. Laws that require mandatory education by pharmacists have given us new motivation to support their needs.

Some impressive collaborative efforts are underway with Pfizer, AADE and American Pharmaceutical Association.

However, these efforts don't begin to cover the need for all pharmacists. Glucose control ranges should be narrowed.

The control ranges continue to be very broad in all levels, low, normal and high.

This begs the question of accuracy of the patient's glucose readings even if all techniques are

perfectly met. Sell the same lot number of strips to wholesalers, as is done with hospitals. This would potentially reduce some of the variability from a consumer perspective.

Reduce the cost of strips or develop and publicize indigent support programs. One of our indigent clinics has an alliance with a company to provide meters at no charge, but more importantly, they have a federal grant to help support the cost of the test strips. Industry and organizations have a great opportunity to work in this area.

Print control ranges on individually wrapped strips or on each vial, not on loose papers that are in the package with the strips. Another area of problem is the area of not cleaning meters. We should have all meters indicate when cleaning is necessary, have optic windows that are durable enough to be cleaned with alcohol, even though they shouldn't be or better yet, have all meters that don't require cleaning.

Another problem area is not enough blood being applied to the test strip and it is a great comfort to see test strips now being on the market that are allowing additional blood to be applied to them. If all the test strips could have that additional second chance to apply

enough blood, that would reduce and eliminate one of the important errors we are seeing.

If less blood were required for the test sample, that would help. If the consistency of the lancing device were improved, that would help with the problem of not enough blood.

Very importantly though, we need to observe patients doing an actual blood test with their meter and supplies at every clinic visit. Meter-to-meter comparison variability is very confusing to patients. If we were able to have all meters consistent in their measurement of either plasma or whole blood, that would reduce some of that confusion.

In lieu of that, education materials that clearly explain the difference -- I struggle with this constantly -- how to explain the difference of plasma versus whole blood and why that difference is okay because that is the testing method.

Patients forget to write down test results, of course, and increasing the number and availability of memory in the meters would help that. The date and time is one of the most valuable things that is available with memory as well.

Another area of major error is interferences from patient conditions, hematocrit, different medications and substances, ascorbic acid, acetaminophen, bilirubin and so on and so forth. If the strips are able to be improved to reduce or eliminate those interferences, that, of course, would help. Meters and strip limitations have been mentioned; humidity, temperature, altitude. If strips can be improved in their viability or if packaging can be improved or if meter cases could be made to help protect a little bit more from temperature, then this would help.

A concern I have in this area as well is related to mail order businesses and we see that coming from Kansas it is going to be a problem if someone is having strips mail ordered to their home and it sits on their front porch in August, when it can be 110 degrees. The strip viability is certainly in question then.

It is difficult also for patients to remove the lids on some of the cans if people have arthritis, neuropathy or poor hand strength. The lids could be improved to help with that problem.

Hitting the target with the blood sample is sometimes difficult. If a more distinct color contrast on the target area of the strip could be done, that would help,

as would help with tactile guides. If people don't have neuropathy, tactile guides on the edge of the strip that is close to the meter target area for the blood sample, that might be an assistance as well.

The customer service that the companies offer is incredible and the customer service number needs to be printed larger and bolder on the back of every meter. That would be a great help in some of the errors that we see.

Data management continues to be an arduous task and the meters need to continue to be able to average apples to apples within the meter in terms of the data management. And the software packages need to continue to be developed that will help with the sophisticated analysis of the overall bushel baskets, if you will, of numbers that patients bring in.

The speed of analysis needs to be improved. Downloading takes a long time.

Meter prompting on testing, on the steps for testing, is sometimes confusing. My experience suggests that if we could use icons instead of words on all the meters, that that would make it much easier for patient use. If we could eliminate the numerical countdown, that would further reduce the confusion.

And, finally, in this area, reporting of data prior to clinic visits for interim adjustments in management is difficult. Some patients try to fax their blood sugars into the clinician for assessment, but if we could evaluate or explore the technology to allow data in the meter memory to be transferred via telephone transmission, somehow electronically, that would reduce a lot of the transmission errors and certainly reduce the time and the labor intensive nature of trying to assess all that.

Some of the additional concerns related to mail order businesses relate to meters being sent to patients and this may not be the purview of this group, but meters sometimes are sent to patients without them requesting it and then that is charged to their insurance. And we are also finding that generic test strips are sometimes routinely sent to patients without any request from them.

Let me conclude my comments in areas of training and access and say that SMBG and suppliers as a part of self-management education are still impaired and that is due in large part to a lack of reimbursement for diabetes education. So, of course, recommending that we continue our work with legislative efforts is important.

Also, training the trainers is an area we would

like to see standardized and with the area of patient performance skills, some consistency there would be very valuable and if we could agree that the items are consistent and that they are all done by return demonstration, that would help.

In summary, glucose meters, patient skills and practitioner expertise have improved because of research and the commitment to offer the state of the art care in diabetes. The AADE position statement on glucose monitoring recognizes that the optimal impact of SMBG upon diabetes control will be reached only when accurate data is obtained. It is consistently applied to an individualized patient-implemented program of monitoring, assessment and decision-making through self-management skills training.

Thank you.

DR. NIPPER: Thank you, Ms. Hensen.

Moving right along, our next speaker on the list is Dr. Robert Ratner from Mid-Atlantic Research Institute here in Washington. Is Dr. Ratner here? Here he comes.

How do we reset the speaker timer? There we go.

The chairman with disabilities act needs a better timer. I had to ask the executive secretary to tell me which color is up there because I am red/green color blind.

So, if the light on this side goes off, I am going to put the hook on you.

DR. RATNER: Fair enough.

DR. NIPPER: Okay?

DR. RATNER: That is fine.

DR. NIPPER: Go right ahead.

DR. RATNER: Dr. Nipper, ladies and gentlemen, thank you for the opportunity to come speak to you.

I am both a clinician, as well as an academician and over the last 15 years of my experience within diabetes, I have served as a consultant to DIVA(?), Berringer Manheim and to Life Scan in various and sundry ways.

I have also been involved in testing of meters and strips and was one of the participants in the 1992 ADA Consensus Conference, as one of the presenters.

Dr. Gutman provided a wonderful overview of the history of self-monitoring of blood glucose, but I think it is useful to take one step further back and remember what self-monitoring of blood glucose replaced and that was urine testing. And I think that that transition is at least part of the reason why we are having so much difficulty today with total error accuracy and precision.

Patients historically had done benedict(?) testing

or urine dip stick testing and gotten a highly variable qualitative assessment of one plus versus four plus glycus(?) uria with very little understanding of what it meant and even less understanding of what to do with that information in terms of making any adjustments in their therapeutic intervention.

When blood glucose testing was initially introduced, most physicians -- and I was fortunate enough to be in that transition zone -- thought it would be impossible to convince our patients with diabetes to actually prick their finger and do the blood glucose testing. The comment was always made, "We can't get them to test their urine and there it is no pain. How are we ever going to get them to do blood glucose testing?"

And, in fact, the medical community, at least outside of diabetologists, were really quite reticent to move to self-monitoring of blood glucose. This was a consumer-driven market. And it was our patients who said we want to know what our glucose is so we know what to do with that information.

So, many of our patients started using visual systems and when you start talking about accuracy and precision there, we were dealing with less than 40, 80 to

120, 120 to 240, greater than 240. Those were the ranges that we had available to us; clearly, a semi-quantitative assessment even then. And yet, it revolutionized diabetes care.

And as we progressively moved to the metered systems so that we have relatively accurate and precise results, we are simply improving on that qualitative system that we have been using for 50 years. How accurate, how precise do these systems need to be?

You have already heard about the diabetes control and complications trial utilizing at least one if not two generations older systems and yet utilizing those self-monitoring systems, we were able to demonstrate that, number one, you could achieve near normal glycemia with a minimal degree of hypoglycemia occurring during that period of time. And as a result, you can minimize complications.

Clearly, we have gone to more accurate, more precise systems since the diabetes control and complications trial was initiated. At the time of those studies, most patients were using systems that required an enormous degree of user intervention, timing, wiping and appropriate amounts of blood. The newer systems in which most of that is taken away from the patient clearly removes the user error

component to an enormous degree.

So, we are moving in the right direction. I think the question before you now is how accurate, how precise do these systems need to be, to be of clinical utility. My own personal opinion is that the comparison to a laboratory standard is both inappropriate and unnecessary. What we are really looking at is a clinical standard.

The limitation in our clinical management of patients with diabetes is not simply knowing what the accurate blood glucose is but being able to do something rational with that information and our interventions currently don't allow that. We can't do minute-by-minute blood glucose manipulation within 5 percent. Clinically, it is not achievable.

What is it that we really need to do? We need to look at systems that are, one, user friendly; two, convenient; three, fast; four, accurate within the range of clinical utility and, five, inexpensive, so that they can be used frequently by patients who need to use that type of monitoring.

I do have an overhead if I could go ahead and demonstrate it.

This is the Cox Error Grid that was published in

Diabetes Care in 1985, looking at blood glucose monitoring, utilizing a reflectance meter, in comparison to a reference range. The intent of these investigators was specifically to look at those errors that would make a clinically significant difference so that the Area A is within 20 percent of the reference range. Anything within that is of no clinical significance. There is no differentiation there. One would never make a change in therapy if, in fact, the value was in either of the A ranges.

The B ranges are in excess of 20 percent error and, in fact, under those circumstances even then you generally would not make any clinical therapeutic change. So that what you begin to see is that unlike the analytic standard of the clinical chemistry lab, one has an almost semi-quantitative assessment of self-monitoring of blood glucose when it comes to the therapeutic implications.

It is only when you get into the C, D and E categories that errors become clinically significant, in which decision-making is markedly impaired. One might choose to make a change in therapy when it would be inappropriate and that change would result in some deleterious effect. So that you are looking at an area now in which we no longer believe or at least the clinicians no

longer believe that the error needs to be within the range of a clinical laboratory.

Clearly, we want the most accurate, we want the most precise data we can get and we hope that industry will continue to move in that direction. But one has to balance that move towards accuracy and precision with convenience and cost.

Dr. Gutman said that three million people were currently using home blood glucose monitoring. That is out of eight million people with known diabetes. If one looks at the frequency of self blood glucose monitoring, it is actually relatively low considering what we would wish people to use.

What are the limitations to people routinely doing self-monitoring of blood glucose? Clearly, one major factor is cost. And as we go to more sophisticated systems with greater precision and greater accuracy, I have little doubt that the cost of those systems will also go up. One has to balance out that increased precision and accuracy with the fact that fewer and fewer people will be able to afford to do the monitoring itself, to have an absolutely perfect system that absolutely no one can afford makes no sense at all.

We need to seek a clinical balance in which patients will utilize the system, get useful information out of that system that can then be translated into useful therapeutics to bring them under better control.

With that, I will end and be able to answer any questions you may have.

DR. NIPPER: We will defer questions or comments until the committee discussion at this point.

Thank you very much.

We will need to reset the wondrous device and while we are doing that, we will -- we will reset it for the speaker after this. While we do that, we are going to be treated to a video presented from Ms. Diane Lellock -- I hope I am pronouncing that correctly -- whose address is Route 2, P. O. Box 381, Punxutawney, Pennsylvania, otherwise known as the home of Punxutawney Phil.

I don't know how good -- how sensitive and specific Punxutawney Phil's predictions are about winter. I hope that the weather outside is getting to be about 50.

Maybe spring is coming around here.

[The following testimony was via video tape.]

MS. LELLOCK: Allow me to introduce myself. My name is Diane Lellock and I thank you for the opportunity of

being able to talk to you today.

A previous commitment has kept me from being there in person, but I thought my message was important enough to bring it to you via video.

I am not a scientist. I am a small business owner from Punxutawney, Pennsylvania. But I am the mother of two diabetic children, ages 12 and 14, and I feel that I am an expert regarding the care of the diabetic.

My son Todd was four years old when he developed diabetes. So, after ten years of diabetes management, we all are well aware of the ups and downs of the disease. My daughter Carlene developed diabetes three years ago. My family has kept abreast of all the current technology available to the diabetic.

Unfortunately, let me say that the in-home diabetes management that has occurred has been minimal. As a consumer, I have taken advantage of the technological devices available in the past years for my children. An example of the technological advancements that have taken place has been a needleless insulin delivery system. It is not perfect and it is expensive, but it does give my children the insulin that they need and it is pain free.

It is a formidable device that gets the job done

without the stigma attached to needles. This is not an emotional plea for advancing technological devices as I do recognize the need for a scientifically-based monitoring system that can be relied upon for accuracy.

I would like to present questions which are in mind and yours as we look at this evolving technology of blood glucose measuring.

What is the current state of the art available for diabetics to monitor blood glucose levels in a home setting? The current technology available today for the consumer to monitor their blood in a home is a device like this. It pricks the skin. It draws blood and you use it on a disposable test strip.

What the diabetic consumer wants and is waiting for is a non-invasive meter that would be accurate, yet painless. Let's discuss accuracy. What is the accuracy of the current technology that is available to us?

The current accuracy of the finger prick technology available today has a margin of error of 20 percent. That is quite a margin considering we base insulin doses on meter readings. A 20 percent margin of error could be crucial to a small child, who bases their insulin needs on the current system.

Let me cite an example of one of my personal experiences with our current invasive system. As recently as January of this year, my children, although seen by a primary care physician here in Punxatawney, Pennsylvania, travel to Pittsburgh, PA, to Children's Hospital. There they see top-notch endocrinologists, who give us the utmost care.

At this appointment, our current system is compared to a laboratory reference monitoring system and it determines the accuracy of our meter. That day we took one meter and we used it for both Todd and Carlene. Our tests were performed five minutes between each child. Remember, we are in a clinical setting. We are at the hospital.

Todd's lab report came back that his meter was working accurately that day. The meter here read 270. The lab results were 310. Using the same meter, the lab report came back Carlene's meter is inaccurate. Please check with the manufacturer. The meter read 252. The lab results read 336. It might be a bit scary because I would have given Carlene too much insulin based on this meter reading.

What elements changed the reliability of the meter in that clinical setting? I cannot answer that. Nor will you probably be able to find any medical personnel who can.

I would like to discuss with you accuracy obstacles. I want to show you that this instruction sheet comes with every box of testers that I purchase and it says my meter will not perform accurately when the air temperature is outside the narrow range of 64 to 86 degrees. So, on a sunny but cold day, I can't use my meter outside. There are extremes in humidity. I don't know. If there is a rainstorm, does that mean it is too humid out?

High altitude. They don't say what level of altitude on the sheet. I just know that if it is high altitude, it doesn't work correctly.

Levels of common aspirin or Tylenol are in their body. What if they are dehydrated? That means if my son is playing basketball and has a lull, I can't test him because I can't know that that meter will be accurate. He probably is dehydrated.

One of the other questions that we are all thinking about is the size of the new current non-invasive technology. The current non-invasive meter is about the size of this box. Do I envision that I will always carry this box around? I think not. Before the laptop computer, the size and the functions of the computer were far different from today.

We finally see computer technology as in all electronical devices. Let us anticipate the same thing will happen in non-invasive meters. But I will tell you as a mother, I would much rather use something large, accurate and painless, rather than something small and not accurate and it hurts.

Let's discuss patient compliance. An ideal system of measuring blood glucose would be a technically superb laboratory with a venepuncture for blood collection.

Unfortunately, this is not a reality. It is not possible and it is not practical for the diabetic. What the diabetic needs is a device with a reasonable level of repeatable accuracy that would encourage them to use it.

No pain. My kids don't want to use this because when they prick their finger, it hurts. They also don't want the associated stigmata of drawing out a body fluid, especially in this age of infectious transmissions.

Let's discuss cost. That seems to be an issue on everybody's mind about the non-invasive technology being so high priced. In the past ten years, I have purchased approximately seven invasive glucose meters. They wear out. They become inaccurate or a better product is brought to the market, but the cost involved can be staggering.

Let's just consider what might be used to get a blood sample; a lancet, a test strip, perhaps a band-aid and in previous years, alcoholate(?), which is no longer recommended because now that interferes with the accuracy of the blood test.

But on an average day with four test strips used per day on each child and only those lancets involved and that is we don't make any mistakes, our cost for last year alone for both children was well over \$3,800. That doesn't include those sick days when sometimes we had to test every hour or if the meter read "error" and we had to use another test strip.

So, the \$8,000 projected cost of the current non-invasive system is a very small price to pay considering the benefits. No pain and no added expense for increased testing. That means we can test all the time and it doesn't cost us anything more.

I am aware of the DCCT, as I think that you probably are aware of that, too, and we all know that that trial encourages frequent testing. I am not a scientist, but I do know the need to verify the promise of any technology, which is introduced.

So, today, my request is your panel provide

whatever assistance is needed in the possible advancement of technology from a painful, sometimes accurate invasive meter to one which will be user friendly and promote my children and the 17 million diabetics across the United States to do a better job taking care of themselves and prevent potential complications.

Please, just judge and review all the technology that is available, invasive and non-invasive, using the same criteria.

On behalf of all the diabetics across America, thank you. And please know that all the diabetics are committed to any advancements in technology and we will be waiting for any future advancements that can happen.

If you would like to discuss this further with me, please feel free to contact me at R.D. No. 2, Box 381, Punxatawney, Pennsylvania 15767.

Thanks, again. And my name is Diane Lellock and I do appreciate the time you have given me.

DR. NIPPER: Okay. After that presentation, we will still need to reset the meter. I apologize for making you start it when we didn't really need to.

Murray H. Loew, Juvenile Diabetes Foundation in New York.

If you forgot that I want you to tell us if you have financial involvement with the manufacturer, please be reminded.

DR. LOEW: Thank you very much, Mr. Chairman.

I am representing the Juvenile Diabetes Foundation today, but I should point out that I have not cleared these remarks with the board of directors of the JDF, but I think I fairly represent their points of view. And I do not have any financial involvement with any companies involved in diabetes care of any sort.

I would like to just review what I am going to talk about. I would like to spend a few minutes on who JDF is, a bit momentarily about the DCCT -- you have heard already about that -- a little bit about glucose monitoring, again, to review some of the high points, what we perceive as the need for more science in this field, the likely prospects for the future that we see coming in the near future -- and Ms. Lellock in the previous presentation made an eloquent appeal that I will follow up on, I hope -- the need for evaluation and the need for the evaluation of evaluation methods and, finally, a recommendation that I think that the JDF would like to make to the FDA.

The Juvenile Diabetes Foundation has represented

Type I diabetics, insulin-dependent diabetics, since 1970 and over that period since that time, it has raised about \$200 million for research in juvenile diabetes.

These funds come from the grass roots, from walk, ride and rolls in neighborhoods to the solicitation of large donors from corporate and other individuals. It sponsors, in addition to research at universities around the country, a number of workshops and conferences. As we speak, for example, in Greece, the Fourth World Conference on Diabetes is going on that is sponsored by JDF bringing researchers from around the world to discuss a number of the aspects of juvenile diabetes.

It is involved in patient education of the parents and of the children themselves and its goal primarily is the seeking of a cure. We really believe that there will be many cures, not just a single one, and some of them, we think, are being discussed here today.

The people involved are the children themselves. They are not exclusively children, but the term "juvenile diabetes" largely embraces children as the principal patients, but some adults do develop juvenile diabetes of the insulin-dependent type.

There are many, many volunteers of parents and

others, including quite a few people who do not have diabetes in the family. The researchers themselves are active participants in the JDF process.

So, again, the goal is to find one or more cures for juvenile diabetes and the DCCT made very clear the importance of control. Dr. Gutman has emphasized this already. Just let me point out a few of the major elements of the intensive management branch of the DCCT trial, which concluded about three years ago. And as you can see, it required very rigorous testing, frequent testing of blood, frequent injection of insulin, the adjustment of those doses in accordance with food intake and exercise and the results of the tests.

The consequences of tight control were remarkable; a dramatic reduction in the risk of the principal complications of diabetes that we all are very much concerned about. So, this impact, this fact then, leads to the desire to monitor blood glucose often. Right now, it is a painful pricking of the finger that you just heard described most agonizingly. And a colleague of mine, who has been a pump user since 1980 made this comment when I told him I was coming here and I think this is not an understatement. This is, in fact, the case, that as far as

an interested diabetic is concerned, to have continuous and convenient -- and those are both crucial words -- continuous and convenient feedback would, indeed, be the biggest advance since insulin.

So, I would like to talk then about this continuous idea. We know that pumps exist for people who want to treat their diabetes aggressively. The fact is, though, that those pumps require input from the user and that input must come from testing. So, we have finger pricks that are painful, inconvenient and take time.

Eventually, if we had some sort of a continuous monitor, we would like to perhaps combine it with a pump to make what is called a closed loop system in which we would measure, we would set a dose, we would measure again, change the dose and continue the cycle continuously in accord with the body's needs.

The problem, though, is that censor. Well, a number of technologies are being proposed and some of them were alluded to in the video, but the technologies for continuous monitoring are all in the embryonic stage. There are some non-invasive ones being proposed, ones that use light, either in the visible or the infrared range; microwave energy as another way to propagate energy into the

tissue and record some changes due to the changes in glucose level; semi-invasive methods that extrude liquid from micropores in the skin and analyze that and, finally, the invasive methods, the finger prick method, which is presently used, and the potential of some sort of an indwelling electrode in a vein or perhaps elsewhere.

A number of organizations, many industrial organizations and some universities are conducting work in this area. Much of the corporate work is development. There is very little applied research and almost no basic research. I believe that that underlies the principal problem, that we have no real successes to date in the non-invasive area and I believe that it is because not enough attention has been paid to the science.

If we have science, we will have reproducibility. In our view, these are equivalent. It is axiomatic. And we are lacking the scientific bases, by and large, to make the steps that we really need to have genuine reliable, non-invasive monitoring.

A lot of the hopefulness that was expressed in the video tape, for example, comes more from hope than from experience. Everyone wants a non-invasive technique, at least many people do, to treat the problems that you heard

so well described.

Well, some alternative approaches in the noninvasive area might be to encourage technology transfer. This is almost heretical when talking with profit-making companies, but I think that there might be a way to do it.

Secondly, that we should require and insist upon peer review, that the results of the various experiments being done by corporate organizations should be submitted to the same scrutiny as is the case with university researchers. The companies, indeed, could sponsor validation studies and if there were some federally-sponsored evaluation, that I will speak of in a moment, I think all companies would benefit from such a program.

Well, a couple of crucial issues. If you are going to talk about evaluation -- and the review that Dr. Gutman gave of the proposed standards was quite comprehensive, but I think that, nevertheless, when one talks about the non-invasive technologies, there will be the need to anticipate problems that are not yet seen. So, we will have to find good evaluation methods for these non-invasive techniques because the number of variables will multiply. It is not going to be a simple -- and it is not simple anyway -- it will not be nearly as simple as the

invasive techniques that are presently being used.

So, we need ways to evaluate and we need then standards for the evaluation techniques. We need possibly a clearinghouse for testing. So, a recommendation that we would offer for your consideration is that the FDA sponsor a workshop specifically to examine the issues and recommend voluntary standards for testing and evaluation of continuous glucose monitoring devices.

We would like to set those aside to distinguish them, the invasive -- presumably invasive, but not necessarily -- "continuous" is the key word -- glucose monitoring devices. The attendees would certainly include the manufacturers, university labs, users, that is to say the patients themselves, industry and professional societies of the types who have been here today and, of course, the FDA.

I think that there would be some de facto force brought about by this, that if people agreed that this was the way to go, even though regulations might lag, there would be some moral suasion made possible.

Well, the number 18 million, 16 million, great numbers have been used, but we do know that there about 800,000 juvenile diabetics who must take insulin and as a

result must monitor their blood sugars.

For many, many years, there have been great expectations raised and every year these expectations are dashed. I think that part of the reason that these expectations get dashed is that they shouldn't have been raised in the first place and the fact that they were raised was due to a great variety of hopes and expectations on the part of corporate sponsors.

If we set some standards and goals and we publicize them widely and we invite all people who would propose to build a machine to meet these -- this same set of standards, we then can have rewards that will be beneficial to all, to the companies themselves and to the patients and their families, who are eagerly awaiting these advances.

Thank you.

DR. NIPPER: Thank you, Dr. Loew.

The next speaker on my list is Madelyn Minch, who is from North Hollywood, California. Ms. Minch, are you here? Yes. We are going to reset the clock for you.

MS. MINCH: Thank you. And it is West Palooka(?)

Lake. They just changed the name of my city for real estate reasons, I think, but it does sound nicer.

I would like to thank the panel for allowing me to

speak today. I have been sitting here all day mostly listening to these discussions and you are talking about my life. I am the real deal. I have ten visual aids, my fingertips -- actually eight because I don't use my thumbs. It might be too far away for you to see, but I check my blood sugar on a -- what some people say fanatically daily basis, but I have my reasons.

I wanted to start by saying that -- oh, I also have to disclose that I don't have any financial involvement, other than I am -- my trip was sponsored by Life Scan today and they are paying me an honorarium to speak, but they think my story is important to hear. I do not work for them and don't own any stock as of yet in their company.

Having said that, my great grandmother, Hannah Minch, was diagnosed with insulin-dependent diabetes and in her town of Red Bluff, they didn't have insulin in Northern California, and so she got on a train to go to San Francisco to get some insulin and passed away on the train.

Her son, David, my grandfather, was diagnosed with insulin-dependent diabetes when he was older and I knew him for about four years of my life until he died of complications from diabetes.

Five years after that, I was diagnosed with insulin-dependent diabetes. It runs in the family. At the time I was diagnosed, there were revelations in the treatment of diabetes; disposable syringes and urine testing. Now it seems all archaic, especially to me in my daily management of diabetes because I don't use syringes anymore. I don't test my urine anymore. I leave that to my doctor. Who wants to test their urine, really?

I would rather prick my finger a hundred times a day than test my urine. And trust me, if you have ever done it, you would want to do it, too.

Anyway, I didn't get my first blood testing equipment, as I call it, until it was too late and at that point it was given to me by a doctor because I couldn't afford it. My insurance didn't cover it and this was in 1987. He wanted to help me with some problems that were starting to occur. It was the tip of the iceberg. I was starting to lose my eyesight and I was on the verge of losing my kidneys.

So, we decided, hey, I had better keep my blood sugar under control. I wish I would have listened to people before this. I wish I would have had more education. I wish I would have had gentler, kinder doctors. I wish I

would have had somebody hit me over the head with a mallet so I wouldn't be standing here today with my sister's kidney -- she gave it to me. I didn't have to take it from her -- and an acute visual impairment.

However, it is workable. It is doable. I am alive and I manage my blood sugar levels today better than I ever have in my entire life. I am within the normal ranges now for the first time of the glycosylated hemoglobin tests. And that is because I have a doctor to work with, that I listen to, but mainly he listens to me and caters to my needs and whims and tests and things like that.

I have insurance now because when your kidneys fail, the government will pay for your insurance, just in case you are wondering how to get insurance. So, I have insurance and I also have an insulin pump. When I wanted to get the insulin pump a couple of years ago, it was not covered by Medicare. It was not covered by the secondary insurance I had to acquire to cover my immunosuppressive drugs, required by my kidney transplant. So, I had to -- and it wasn't covered by any forms of my personal insurance.

So, I had three insurances and it was covered. I got together with the company and they worked together with me in getting MediCal to finally accept coverage in

California. Since then, it has made my blood sugar control better, but more importantly my quality of life. It is not just the quality of the machines being available and the accuracy and all that stuff is, of course, important -- and I can reiterate everything everybody has said up here because it is all true and it is all important, but it is the quality of life. Nobody wants to sit at home because their blood sugar is too low or their blood sugar is too high.

Nobody wants to get up in the morning and think about, let's see, I would like to do this today but how much insulin am I going to need to do this. How much time am I going to need to have my insulin be absorbed into my body? These are things that people without diabetes don't have to think about, but this is what I have to think about on a daily basis. With my blood testing equipment, I am able to do what I couldn't do when I was a kid. I can adjust my dosage anytime of the day I want to because I am wearing an insulin pump and I have got quick results, accurate results, dependable, readable results on the blood testing equipment that I use.

I can't tell you how it has changed my life. It used to be when I would travel, and I did say that I

traveled from California, traveling would always screw me up. It would take me a couple of days. Sitting on the plane yesterday, I knew I would be sitting there. I was able to adjust -- pull out my pump -- maybe you haven't seen one before, so I do have another visual aid -- I was able to pull out my pump and program that I wanted the duration of the flight to give me a little bit of extra insulin because I knew I wouldn't be walking around and, therefore, the food that I ate and things like that would just be sitting around in my body.

Anyway, I am kind of rambling and I just wanted to tell you that there are people, millions of us, like me -- I guess I am representing them -- I didn't know I could have sent in a video. I might have stayed in California where it is 95 degrees today. But this is a great opportunity to see your faces and for you to see mine.

My friends call me Matty. So, when you are making decisions about improving the technology, maybe keeping some technology the same, going forward, staying where you are, whatever decision you are going to make, maybe you will remember Matty. Maybe you will remember the millions of Mattys out there who are living with diabetes, living proof that testing your blood sugar and watching your insulin dose

and managing, self-management with the guidance of a doctor, is the only way that you are going to be able to stay off the complications.

I do have to add one more thing, that since I have been on the insulin pump, next week I will celebrate six years with my kidney transplant. My creatinine is 1.1, thank you very much, and my eyesight has greatly improved. I do not need to use a cane. I can read large print. I still can't drive, but that is probably a good thing for everybody else on the road.

Thank you very much for your time.

DR. NIPPER: Thank you for coming all this way to tell us your story.

MS. MINCH: You are very welcome.

If anybody has any questions, please let me know.

DR. NIPPER: Thank you.

If you will permit me a personal comment, one of the reasons that I, and I think I speak for many of my fellow professionals in the laboratory that I know personally -- one of the reasons I went into clinical chemistry was that there are Mattys there that are at the end of what I do everyday and I think most or all of us on the panel are here because we want to make things better for

the patient.

We at this time have a letter that Sharon is going to read from another person who submitted information to the panel.

MS. LAPPALAINEN: As we have time permitting in the public session, I received a letter from Frank and Dina Econamides(?). It is addressed to Ms. Sharon Lappalainen, Food and Drug Administration.

It goes something like this: Thank you for inviting me to speak regarding my father, Ulysses G. (Blackie) Auger(?) and his battle with diabetes. Unlike many families who were raised with the knowledge that diabetes existed in their family, this was a disease that was unknown to us. This was something that we had heard about but never felt that it would exist in our family until four years ago when my father was diagnosed with pancreatic cancer.

This operation left him with a total of 15 percent of his own pancreas, which produces minimal amount of insulin. Immediately, the family was in shock with the significance of insulin in the body and how it affects a person and his or her lifestyle and eating habits. Little were we prepared for mood swings that are created due to the

amount of sugar, whether high or low, the amount of pricking of the finger and the injections that are needed to be taken.

Granted, it would take a day to tell you not only his suffering but the family's suffering as well. Over the four years, we have become our father's doctor. We can tell before him whether he needs to take his sugar and many times he refuses because 30 minutes earlier he checked it, but we as a family know that he is still shaky, he is wobbly, his face is red and that he must have received a false positive reading. And we need to convince him to take it again.

My father also has Don(?) syndrome. This means that in the middle of the night his sugar dips too low and he cannot feel the difference, but my mother can tell the difference. Many a time they argue for him to prick the finger to check his sugar and he refuses.

As you know, many people with this syndrome die in their sleep if no one is around to wake them to check their blood.

The DiaSensor(?) 1000 could save his life in these instances. He would not hesitate checking his sugar during these nights and many times over to keep his eye on the sugar. More importantly, should my mother ever question it,

she also just placed his arm over the DiaSensor 1000 to obtain a reading.

There are other instances as well. As I have learned to become a doctor myself, I find that should he eat, prick his finger and check his blood, most likely he would receive a false positive reading. Ten minutes later he would have to check his blood again to verify the reading. Much of this playing doctor, questioning which is or is not the false positive reading, could be less painful and more accurate with the use of both the pricking and the DiaSensor 1000.

We recognize that in years to come the DiaSensor 1000 can only become better and more important than it is today. Life with diabetes is as if you are constantly carrying your burdens with you and making every effort not to lose one's own identity to the disease. We support BioControl Technology, Incorporated for its role in assisting people with diabetes and creating the DiaSensor 1000 to help bring normality and safety back into people's lives.

Thank you very much for the opportunity to tell you the good this type of research does and the importance of it for people who are diabetics and also how it can help

the family as well.

The letter is signed "Dina Auger Economides," a stockholder with BioControl Technology, Incorporated.

DR. NIPPER: Okay. At this time we are at 3 o'clock and between now and the 3:30 break, the committee will have a discussion of the clinical issues in open session.

Agenda Item: Open Committee Discussion

We can start with either end of the table and go around and discuss the issues involved, including, I would presume, questions of any of the presenters that we desire to ask questions of.

I am going to start -- instead of at the end of the table today, I am going to start in the middle.

Dr. Goldsmith is easily accessible. I am probably not out of striking range here. Do you have issues that have been brought up in the public session or issues in the document that you would like to discuss or raise at this point?

DR. GOLDSMITH: I have a question certainly and I am sure I will have other issues as we move forward.

Certainly, from my perspective in a pediatric institution, I saw in the document there were several

comments about the neonatal use and that there was a neonatal guideline. I don't see it. And I was wondering if perhaps we can address -- since certainly the pediatric use of glucose monitoring is addressed at all times -- I was wondering, Dr. Gutman, if you could expand on that.

MS. ROOKS: Hi. I am Cornelia Rooks and I am with the Division of User Programs and Systems Analysis.

There is currently a neonatal document and I am not sure that it is available yet, but there is currently one.

Sharon, do you know for sure whether it is available? I don't think it is yet.

But if you do have comments, we welcome them as well.

DR. GOLDSMITH: Once I see it, I probably will.

I guess I am bringing that up because we, as I have said, have talked a lot about the uses in both the pediatric and the adult population and there are differences clearly in using blood glucose monitoring and Dr. -- I am blanking on the name, but the first person who addressed us -- Dr. Ross from the CAP talked about AST and the use of blood glucose monitoring in the hospital and the need for certainly even more aggressive both education, quality

control, quality assurance, et cetera, and there are certain meters that have been approved in the neonatal environment and others to this point have not.

So, I think it would be helpful as we define this to incorporate that.

Those are my comments right now.

DR. NIPPER: Dr. Cooper.

DR. COOPER: I don't have any comments at this time.

DR. NIPPER: Dr. Zawadzki. It is early in the session but we have a few minutes for concerns that may have been raised by the speakers.

DR. ZAWADZKI: I was just thinking about the issue that Dr. Ratner raised about the prevalence of the use of monitoring, that three -- I think Dr. Gutman had quoted that three million individuals had or used glucose meters and that represents less than 50 percent of the known number of people with diabetes.

I think that is an important issue to consider. Number one, do all people who are diagnosed with diabetes need to monitor and is that our whole sample size that we are addressing or are we addressing different groups within that sample size and, therefore, the needs of those

different groups are very different and, therefore, the meters that might be needed by the different groups also differ?

Just a thought at this point.

DR. NIPPER: Thank you.

Dr. Kurt, do you have something you would like to raise?

DR. KURT: I don't have anything additional to add at this point.

DR. NIPPER: Okay.

Dr. Rosenbloom.

DR. ROSENBLOOM: A couple of comments.

One is I think Dr. Zawadzki's comment about the type of diabetes and the numbers is very important. We have heard everything up to 17 million people with diabetes, which is pretty dramatic incidence, prevalence, I should say. There is certainly a large number of people with diabetes who don't need to be monitoring their blood glucose four or five times a day. And there are a large number who do. But I would appreciate Dr. Clement or Dr. Zawadzki, particularly, Dr. Cooper comment on the adult population with diabetes and what portion of that population really needs to be monitoring intensively.

That might be a population who could get along very nicely doing a bi-weekly fructosamine or daily blood glucose monitoring or even urine testing might be appropriate in some of those individuals who are reticent about sticking their fingers.

So, I think the diagnostic category is very important. There is probably about a 150,000 pediatric patients with diabetes in this country, but that isn't the entire, quote, Type I or juvenile diabetes population because, obviously, most children with diabetes, happily, grow into adulthood, survive and many of them into middle age -- most of them into middle age and many of them into old age. So that there is probably a total of about 800,000 to a million Type I patients and the other numbers that we hear are expandable or contractible, depending on how many undiagnosed patients one is talking about and so on. When you hear about half of the diabetes population in the country is undiagnosed, that isn't Type I diabetes. That is Type II diabetes and their monitoring needs may be considerably different.

So, that is important and that flows into the question of clinical accuracy as well. I believe that is an important concept that Dr. Ratner brought out. We heard the

eloquent and concerned mother talking about 20 percent accuracy as if this were some kind of inherently evil situation, which in general it is not. And even the instances she cited would be unlikely to lead to errors in decision-making. Where we see the problems are with -- when people are getting consistently low values with machines that haven't been checked or with techniques that are inappropriate and making decisions that are inappropriate in that manner.

Then one more comment about temperature and humidity. My associates at the Diabetes Camp a couple of years ago did a very nice study in Florida -- the question was raised by the mother again about what is humid. Well, Florida in August is humid by definition. You don't get more humid than Florida in August except when it is raining, which it often does.

It also defines "hot," Florida in August. And they tested -- I can't tell you which meter, because I don't recall, but they tested the system in that environment and there was no difference between air conditioned, relatively dry environment or out in the cabins in the heat and humidity.

So, I think the systems are reliable. I don't

know how much data exists or is available to FDA, but our experience is that the system -- at least the particular system that my colleagues tested was reliable under those circumstances. That has been published in Diabetes Care.

DR. NIPPER: I have a follow-up question. I would like your opinion, Dr. Rosenbloom, on whether the -- on the Cox diagram from 1985, and whether or not that is still the standard of care or whether other M.D.s here might be willing to comment on that. In other words, have things gotten tighter than the Cox diagram?

DR. ROSENBLOOM: I think the meters -- there are meters that are not terribly reliable that we just don't use. There are a couple of meters that we trust. Those are the ones we recommend. We trust them because they are relatively easy to use and because their accuracy has been demonstrated.

I believe that the accuracy is better than it was in 1985, but that diagram is -- it is useful as a concept, but we don't use it in any way.

DR. NIPPER: My question directed at the rest of the panel members who treat diabetes patients is the implication is that if it is plus or minus 20 percent, plus a wider range around that plus or minus 20 percent -- and,

Dr. Ratner, correct me if I have interpreted something you said incorrectly -- then the clinical impact is minimal.

So, I am wondering if we need to get more accurate. I think that was Dr. Ratner's implication, whether there are other areas that we need to go in dealing with with these issues.

DR. ROSENBLOOM: Well, there certainly is one area where we need to be extremely accurate and that is in the neonatal and in hypoglycemia in general, but even a 20 percent error rate if you are talking about whether a child has a blood sugar or a patient has a blood sugar of 60 or 72, it does get a little bit concerning if you are talking about 40 or 60.

But in general, a 20 percent error, maximum error, is acceptable. But I would be interested in other people's comments about whether they think that the accuracy, because of the easier handling and timing and so on of the contemporary meters, if the accuracy is better. My impression is that it is.

DR. NIPPER: Why don't we move along this side.

DR. RATNER: May I respond?

DR. NIPPER: Please do.

DR. RATNER: I think the important aspect of the Cox Error Grid is not to be used with the patients per se,

but rather for clinicians or investigators to examine the meter systems themselves. And I would agree entirely with Dr. Rosenbloom that in the last 12 years, the range of accuracy has gotten tighter and tighter and we are doing better than we had before.

The implications of the Cox Error Grids are purely clinical. The issue of what would you do with the data --

DR. NIPPER: That was the thrust of my question.

DR. RATNER: Absolutely. And I think that is the whole issue here.

As our therapeutic interventions get more precise, then we will require more accurate blood glucose measurement, but right now we have such incredibly poor therapeutics, even with the insulin pump -- it is a very coarse therapeutic intervention -- that to have greater accuracy doesn't translate into greater effect. I think that becomes the issue.

DR. NIPPER: Thank you.

I wanted to raise that issue because I think it is a very critical issue. The other reason I wanted to raise that same issue -- and then we will move over to this side of the table -- is that there are all sorts of other uses of these devices that are at the edges or the envelope and some

of those uses that particularly have been raised by Dr. Ross demand accuracy and precision that is equivalent to the hospital laboratory when they are used at the bedside in inpatient areas.

So, we have a multiple -- a hydroheaded monster -- is that a bad analogy? -- a multiple use problem.

Dr. Rej, do you have issues you would like to raise?

DR. REJ: I think I would like to underscore the fact that I agree that clinical needs should be the driving force in the decisions here, but I worry a little bit that a lot of that is somewhat subjective, the discussions that took place previously regarding these error grids and one person's clinical feelings may be different than another's and there is some subjectivity there.

While it would be wonderful to have all of these meters be exactly equal to the best laboratory-based systems, if that were possible at low cost, there would be no argument. Everybody would absolutely agree with that. The question is what clinical criteria are really desirable and I personally have a bit of a problem, even though the clinical treatment would be identical, let's say, at a glucose level of 300 and 600, I would be uncomfortable

approving a device as safe and effective if it couldn't tell the difference between 300 and 600, even though an error grid analysis might say this is a very low risk error.

DR. NIPPER: Or at the low end, if you couldn't tell the difference between 40 and -- or between 30 and 70.

Dr. Boughman.

DR. BOUGHMAN: I would like to defer to Dr. Clement because I think he had some things to add on the clinical interpretation.

DR. CLEMENT: It is tough being on the end at this discussion after, you know, hearing all these issues.

The answer to Dr. Rosenbloom's question, I think Dr. Ratner may be able to have some input on that, too, because we are friends and also professional colleagues in many different ways, even though we sit on different sides of the table at this meeting, is for the adults with diabetes, I think now we are going to -- that almost everybody on any type of medication with diabetes should be monitored, regardless of whether it is insulin, whether it is regards to an oral agent. I think that is even becoming more an issue now that we have a new drug out called Troglidizone(?), which we now have the potential advantage that we can probably almost near normalize glucose levels

with either that drug or a combination of that drug and other oral sulfanurias(?) or with insulin and almost the entire population of Type IIs, which we previously did not have within, you know, even three months ago. And now that we know based on DCCT and, obviously, other large population data that it really is the person's long term exposure to glucose, which is the proximate cause of our long term complications.

Any way that we can find so we can monitor a person to get their sugars as close to normal as possible, then the patient is going to benefit. Obviously, the closer we get to that goal, the closer to the edge of hypoglycemia we get as well. So, that also brings up the issue on accuracy.

Dr. Rosenbloom mentioned about the issue of accuracy as Dr. Ratner did as well. I am intimately familiar with the Cox decision analysis because we actually use that when we are basically field testing an in-hospital-based machine several years ago and do we have that up here -- could we put it back up, Bob?

While he is getting it, one of the things that came up with it -- and I think it does have some rational points to it -- is that it shows that the higher end of the

sugars that a person has, there is less error that can be made. In other words, for example, if you are using a sliding scale on someone on insulin, if their sugar is up 300 versus 400, that is greater than a 20 percent change in accuracy, but the actual decision that is made is probably going to be not that much different.

I do agree with when you get to the higher ranges that Dr. Rej said, but if you are using an algorithm for insulin sliding scale and you get a 300 and your sugar is actually 600, then that could potentially be a problem because if your sugar goes to 600, you are probably very close to DKA. You should be monitoring ketones, calling your physician, probably calling 911 or getting to the emergency room.

So, I think on the upper end there are problems as well, but one thing that this model has that is very close to the standards that are used by the FDA now are that in this range, as you can see, these lines actually converge. So, that means these errors are actually -- have to be tighter or the tolerance for errors is tighter on the low hypoglycemic range. And, so, from that point of view, I think this decision analysis is very helpful, but actually in this range if -- I have to actually do the arithmetic --

I think it is within 20 percent over here or close to about 20 percent.

It is just as the blood sugars go higher, it leaves more of a tolerance for inaccuracy, so to speak, between the patient's glucose meter testing and, for example, the lab reference method. The ones that, obviously, I am more concerned about from a personal point of view on immediate danger to the patient are the ones that are called D and E range and these type of ranges, the person's meter shows either a normal blood glucose level or a high blood glucose level, but in actuality they are both glycemic and the patient's actual blood sugar level is 50 or less.

Clearly, in that type of range, there could be a problem and from that point of view -- is Matty still here?

I wanted to ask you a question. You mentioned a lot about your meter and also about your pump and that you couple your results of your meter to your pump. How do you do that?

Can you -- do you have algorithms or things that you use?

MS. MINCH: Your question was how do I adjust the dosage of my insulin and all that sort of stuff?

DR. CLEMENT: Yes, basically, particularly coupled with your readings that you get yourself.

MS. MINCH: Yes. I have this magic eight ball and I just kind of -- no, I am sorry. We do a thing called carbo counting. So, when you first get your pump, you get a lot of literature along with it or you can request it and you get a diabetic educator to kind of train you on it. So, I requested a lot of different literature about it. One showed you kind of a starting range for the carbohydrate count. So, if you are going to be eating carbohydrate, when you do your bolus, which is, in effect, giving yourself a shot, you know about how much to program in and then you also factor in are you going to be exercising afterwards; is it going to be at night.

There is a lot of things involved. Then over a period of time you realize what your body does with insulin because everybody's dosage is different. You work with your doctor that way and you also -- trial and error. But find out that maybe if I am going to be sitting down, I will need this amount of units per insulin and you can have a -- I don't know if you know how the pump works or not --

DR. CLEMENT: Of course.

MS. MINCH: It is this pump. Well, I meant you --

DR. NIPPER: Not everybody does.

DR. CLEMENT: Right.

MS. MINCH: You invented it, I know. But it is a slow drip of insulin, a continuous drip of the insulin. So, you can program it to change drips without you having to actually pull it out and change it for a 24 hour period. Through trial and error, I know what my blood sugar is like when I sleep, what its patterns are when it goes up and when it goes down because the first week or so I had it, I would wake up about every hour or so and test my blood sugar and then I would see from that and depending upon if I have pasta at night, just things like that.

I mean, am I overly answering your question, which I am prone to do?

DR. CLEMENT: No. I think that is very helpful.

It is very important for the panel members because there are only about three or four of us who are clinicians that basically -- you were saying you are a partner in this whole process with the physician that sits and listens and figures out how this will work and --

MR. MINCH: Well, and he reads every single thing that comes out and he will fax me a copy of it, which half of it I would have to take out a scratch paper and a pencil and try to decipher what it means, but some of it I can kind of get the gist of. If not, I just nod when he is

explaining it to me and then say now tell me what it really means. As far as like this chart and the graph and the area you are talking about now, I was just back there kicking myself because I was going to mention that my doctor and I talked about testing your blood sugar, what ranges -- what the studies show your ranges should be in and what he says your ranges should be in and also the percentage difference.

The same as Dr. Ratner was saying is that the percentage difference is so -- is within the same dosage range, like that 10 percent, that 15 percent, which I have never heard of the 20 percent before, but I heard it was somewhere between 10 and 15 percent and it has been when we have checked my meter against the doctor's blood test. But in the ranges that my doctor and I are trying to keep my blood sugar in, that wouldn't matter whether it fluctuated that much, whether it was that accurate or not because it is the same. It is the data. It is the information. It is the patterns and if you are up around 300, that is an entirely different treatment than if you are at 150.

So, as you see your blood sugar creep up, which I do, it is rare that I would just find from one minute to the next I have a really high blood sugar, especially with the

continuous flow of insulin in my body, but that is what that means to me. That is how I have treated that.

DR. CLEMENT: Thank you very much.

MS. MINCH: You are welcome.

DR. NIPPER: Before you sit down, Dr. Clement, I am curious about the low end of that chart, where the road widens out --

DR. CLEMENT: Right here?

DR. NIPPER: Yes.

DR. CLEMENT: Why does that occur or --

DR. NIPPER: No, not why does it occur. Why is it okay to widen it out like that? Because I have seen bedside glucose meters that go haywire down that end that caused us big problems in the hospital, where we were getting inaccurate bedside readings and accurate lab readings and the patient was in the middle.

DR. CLEMENT: I think when this paper first came out -- I think it is even addressed in the paper. It has been awhile ago. The rationalization on having it widen out like this is that once the blood sugar is detected as being low, i.e., less than 70, it doesn't matter whether it is 70 or 30. You are basically going to take the same treatment. In other words, for example, if --

DR. NIPPER: Is that a widely accepted consensus?

That is outpatient and not inpatient, right?

DR. CLEMENT: If it is 20 and the person is still awake, you may give a little bit more glucose than if it is 70. Actually, that may be changing because now with intensive management, it is not uncommon -- and Dr. Zawadzki, I am sure, had several patients, can comment on this as well -- that sometimes we may if a person is able to tolerate and very sophisticated, we can -- they are reliable and we know that they will be testing frequently, we may ask them not to treat a 70 in that that is actually a normal sugar.

DR. NIPPER: But what if the meter says 70 and it is really a 30?

DR. CLEMENT: Then that could be a problem.

DR. NIPPER: Right. Are you talking about adults only or are you including children in that?

DR. CLEMENT: I take mainly care of adults, but I am sure Dr. Rosenbloom can comment on that.

DR. NIPPER: The problem that Dr. Goldsmith and I are thinking about is neonatal intensive care units and stuff like that.

DR. ROSENBLOOM: Not just neonatal, but certainly

the pediatric patient who may fluctuate more and may be going out to play. We would expect the 70 to be treated with a snack before they exercise, but it might not be.

They might say, well, that is fine. My sugar doesn't go down when I walk to the store and back, but, in fact, it may be 50 or 40 and down there, the accuracy has to be fairly high if decisions are going to be made, particularly -- mention was made of the pump but we use very few pumps in pediatrics, but what we are using a lot of is LisPro(?) and those decisions tend to be very tight around the normal blood glucose levels.

So, I think that when you get into the normal and hypoglycemic range, we demand a greater accuracy than we did in 1985.

DR. NIPPER: Dr. Harrington Falls, do you have any comments or questions to add in our waning moments here?

DR. HARRINGTON FALLS: I had a few comments.

This reminds me of the observation that anybody that owns two watches never knows what time it is. With the monitoring, it seems that we are talking about is this an accurate result and exactly what are we going to base our treatments on.

The personal stories were just very gut-wrenching

to me, the devastating effect of this disease on not just the individual person but the whole family. It really enhances my commitment to treatments.

Anything to try to help people to stay in good control and minimize complications -- I think the discussion of monitors is going to help with that. In obstetrics, any woman that can become in good control before she conceives, the risk of fetal anomalies and so forth is going to be reduced. I hope that this will be a good educational and a treatment breakthrough.

But I am concerned also in hearing some of the patients affected really going on about, you know, I am my own doctor and, again, it is the team approach. We need to hear their feedback as to what they are seeing day to day, but they also need to understand that they are not alone in managing this and the family that the father had pancreatic cancer and subsequently developed insulin-dependent diabetes, made me feel like they felt that they were alone in the management of it.

DR. NIPPER: Ms. Rosenthal.

DR. ROSENBLOOM: This is for Dr. Ratner and if I understood you correctly and if I did, it really strikes a chord. You indicated that you felt that we need different

clinical -- different standards for the clinical situation than for the laboratory. I am assuming and I may be assuming incorrectly that what you are saying is that the way the patient needs to monitor themselves or the results the patient needs to seek through his glucometer do not have to be as perfect as what you would want in a laboratory.

I couldn't agree more with you and I think, obviously, Dr. Rosenbloom also agrees. I think the 20 percent is acceptable. I am the parent of a diabetic child and I did put something -- I would like to read something that I wrote to Sharon, if that is okay, in my considerations. And I said, simplicity, simplicity, simplicity. That indicates ease of carrying device, the easier the use of transportability of the device, the more frequently a patient will be willing to test their blood.

That raises the question. Is it acceptable to sacrifice some accuracy in order to encourage more frequent testing? As I say, I am the parent of a diabetic and until I sent her off to college, she would have answered any question about how frequently she tests with as often as my mother has an anxiety attack.

I believe that the more frequent testing is what renders the better result. And I would like to -- do agree

with you that we need to set different standards for the clinical setting than for the laboratory.

DR. NIPPER: Dr. Habig.

DR. HABIG: I think it is important to remember that we are talking for the most part here about the self-monitoring of blood glucose. When Dr. Ross made his presentation about alternative site testing, he actually used the phrase "diagnostic procedure" and that is what a laboratory does but that is not what typical over-the-counter glucose meters are labeled for nor cleared by the FDA for. They are not a diagnostic procedure. They are a self-monitoring blood glucose procedure and, in fact, the people who expect those meters to give laboratory quality results are looking at, in fact, apples and oranges.

It really would be nice if we could have an inexpensive meter with an inexpensive strip and inexpensive controls, easy to use. And manufacturers, I think, are all working toward that goal. Whoever gets there first is going to do better than the people who follow.

The non-invasive kind of meters are what diabetes people are really looking for; no blood, no pain, but, yet, inexpensive, convenient and all the other things. I guess my main point here is that self-monitoring of blood glucose

sort of is by definition sequential monitoring by a patient for their care in consultation with their health care team. They are not designed nor labeled to be one time accurate glucose testing, even when used at the patient bedside in the hospital.

DR. NIPPER: Thanks, Bob.

Dr. Zawadzki.

DR. ZAWADZKI: I would just like to extend the discussion about hypoglycemia because I think that is probably the single most important issue regarding monitoring and the safety of monitoring. I think, first of all, one very important clinical consideration to remember is that individuals who do participate in intensive regimen usually become less aware of symptoms associated with hypoglycemia, so that the variation between a 70 and a 30 becomes even more important.

And yet some of us are probably a little bit more conservative in our clinical approach than others, but I think it is important to, first of all, instruct anyone who uses a meter that it is only a tool, that it isn't as good as the body can do. With that consideration, I think one has to also consider, again, the issue that I brought up before, that different meters might be appropriate for

different settings, that the standard one expects in a hospital lab fall into one category, than the standards that one expects from a hospital bedside meter might fall into a second category, but perhaps the clinical use of a meter might be a different category again because patients are expected and I assume are usually taught that there is a greater variation and that they are taught to be more cautious when they are caring for themselves.

Whereas, the onus for care falls more on the hospital in terms of the laboratory medicine and the point of care method in the hospital itself. So, you know, I think those are important considerations that really might differ in terms of using this kind of a grid.

DR. NIPPER: Thank you very much.

The hour is just a couple of minutes past the time for our break. We have had one of the most interesting -- speaking personally, one of the most interesting and informative two and a half hours I have spent with the FDA. I particularly want to thank Dr. Ross, Ms. Hensen, Dr. Ratner, by way of video, Ms. Lellock, Dr. Loew and Ms. Minch, our letters and video that we had, I thought, were very helpful.

I would like to thank the panel members for their

input during this last half hour or so. Particularly, I would like to thank Dr. Alpert and Dr. Gutman for getting us off to a good start.

After we have had about a 15 minute break, we are going to have two other presentations from FDA employees about various aspects of this problem, followed by an additional open committee discussion.

Hang in there folks. Have some stamina. We are on the right track here and I will look forward to seeing you in about 15 minutes.

[Brief recess.]

DR. NIPPER: I would like to bring the audience up to speed with a little bit about what we are trying to do and we will be bringing the panel up to speed at the same time because something got left out of our packets.

We sort of accidentally did Goal No. 1 during that first half hour, which was to identify how patients are currently being managed. So, actually the panel did a good job of doing what it was supposed without knowing we were supposed to do it.

But in the interest of trying to get to do a better job of knowing what we are -- doing what we are supposed to do, I would like to tell the panel and the

audience in advance that we are also being asked to determine what goals are appropriate for different groups of patients and different treatment regimens.

Now, I would assume that that is not only selfmonitoring on an outpatient basis, but I have noticed that
in the definitions in the review criteria document that we
have in front of us as the panel members, a definition of
"portable blood glucose devices are intended for use in
hospitals, at point of care and physicians' offices and over
the counter."

So, this is an all-encompassing definition of the devices we are looking at, not just for self-monitoring by diabetes patients.

Then the other goal for this afternoon is to determine what device performance is needed for support of the goals for the different treatment regimens are that we are going to look at. We may or may not get to these today, but I would like for you to think about them and we will try to direct our discussions at them so that we at least tiptoe around them if we don't assault them head on.

Also this afternoon we are going to be treated to two presentations. The first of these -- and, Ms. Dillard, I am sorry we are starting a little later than I wanted to

-- by Sharon Dillard, who holds a master of science and alphabet soup afterwards. She is in the Division of Postmarket Surveillance, Office of Surveillance and Biometrics, Center for Devices and Radiological Health.

She is going to give us a presentation on medical device reporting. Ms. Dillard.

Agenda Item: FDA Presentation -- Medical Device Reporting

MS. DILLARD: Mr. Chairman, distinguished panel members and members of the audience, today, I have been asked to provide you with information about adverse incident reports submitted to FDA that involved alleged failures or malfunctions of self-monitoring blood glucose systems.

As Dr. Alpert and Dr. Gutman have previously stated and as other speakers today have clearly pointed out, self-monitoring blood glucose systems have revolutionized the care of and substantially improved the quality of life of millions of diabetic individuals.

It is estimated that hundreds of millions of blood glucose meter measurements are made every year in home use and various health care settings. Patients and their care givers depend upon these measurements to make real time adjustments in diet or therapy regimes. Failures or

malfunctions of blood glucose monitors that result in erroneous readings can, if acted upon, have both immediate and long term adverse health consequences.

Accordingly, FDA becomes very concerned when these medical devices allegedly malfunction in their intended use setting or otherwise fail to meet their labeled performance specifications as the public health impact of such failures is potentially so great.

In order to present the reported information involving alleged failures and malfunctions of blood glucose monitoring systems in its proper context, it is important to begin by providing you with some basic information about FDA's adverse reporting program.

With this in mind, the objectives of my presentation today are as follows: to provide you with a very brief overview of our mandatory and voluntary reporting programs; to discuss and make you aware of limitations and strengths of the information contained in the adverse event reports we receive and to provide you with a summary of information contained in adverse event reports involving self-monitoring blood glucose systems.

FDA's adverse event reporting system consists of two parts; a mandatory reporting program, as described in

Title XXI of the Code of Federal Regulations, Part 803 and titled -- and I think it is very creative -- "Medical Device Reporting." The Medical Device Reporting or MDR regulation requires medical device manufacturers, distributors and user facilities, each with their own set of reporting requirements, to submit reports to FDA when they become aware of certain types of adverse events involving medical devices.

In addition, FDA maintains a voluntary reporting system that is available to health care professionals and consumers. What types of information is reported to FDA? Under the mandatory reporting program, the MDR regulation requires medical device manufacturers, distributors and user facilities to report in certain cases when the failure or malfunction of a medical device caused or may have caused a death or serious injury or illness or whether or not the device in some cases when it malfunctions and it may have caused or contributed to a death or serious injury were that malfunction to recur.

It is important to note that under current FDA reporting requirements, adverse device events that meet the mandatory reporting thresholds, even if such events are attributed to user error, must be reported. FDA also

recognizes that health care professionals are often the first to recognize problems with medical devices and that some reported or some problems that occur that may not require mandatory reporting have a significant clinical impact and, therefore, the Agency maintains a voluntary reporting system, which is available 24 hours a day that can be used by health care professionals and consumers.

Under the voluntary system, any type of medical device problem or concern can be reported.

An injury that may be serious to me may not seem very serious to you and vice-versa. One of the most important concepts to understand with respect to FDA's mandatory adverse event reporting regulations is that there is a very specific regulatory definition for what constitutes a serious injury.

FDA defines a reportable serious injury or illness as one that is either life threatening, results in permanent impairment or damage to body function or structure or requires medical or surgical intervention to preclude permanent impairment or damage to body structure or function.

Although this slide appears complicated, it is intended to illustrate that FDA's adverse event reporting

system is structured as a feedback mechanism that captures information on emerging medical device problems and it has a mandatory and a voluntary component. Adverse event information submitted to the Agency from any source will flow via defined regulatory mechanisms between FDA, medical device manufacturers, user facilities, health care professionals and consumers.

If you could change that slide back for just a second.

The reported information is used to help FDA identify and address emerging postmarket medical device-related issues and as appropriate, FDA can investigate and communicate important information regarding significant device-related public health matters to the device user community and consumers.

The Agency issues such communications in the form of safety alerts, medical alerts, public health advisories, patient notification and classification of product recalls.

Next slide, please.

On the average, 100,000 adverse event reports involving medical devices are submitted each year to FDA.

To use this information appropriately, one must clearly recognize the strengths and the limitations of the reported

information contained in the system. When used in its proper context, FDA's adverse event reporting system for medical devices is considered to be one of the best of its kind in the world.

Our clinical experts and scientists use the reported information to assist them in identifying both emerging medical device-related problems and previously unrecognized public health concerns associated with the use of medical devices. And the reporting system has been a great success. Information reported to FDA has proved to be a unique and powerful tool that has assisted the agency in recognizing and addressing a number of important medical device-related issues.

At this point in the presentation, I would like to ask that you resist the temptation to treat the information that I will be summarizing from the adverse event reporting system as data obtained from a well-controlled clinical trial. Compared to data obtained from such trials, the information in FDA's reporting system concerning alleged medical device-related problems has important strengths and certain limitations that must be carefully considered.

FDA understands that for the most part the information submitted to our reporting program consists of

unconfirmed allegations. The events typically and the text provided along with the event reports contain very little information that would allow one to make a definitive cause and effect determination regarding a given event. And the Agency recognizes clearly that there is great variability in mandatory and voluntary reporting practices.

There is underreporting as the result of noncompliance and lack of understanding or awareness and there
are also biases that result in increased reporting for
certain types of devices or device categories. And examples
of this would include press coverage, publications in the
medical or popular literature or, in some cases, a recent
FDA inspection.

As a result, the reported information cannot in and of itself be used to determine or otherwise predict the incidence or prevalence of any given device-related problem or failure mode nor should it be used as a marketing took to differentiate, quote, good firms or products from, quote, bad firms or products.

With this said, from this point on in my presentation, I will be discussing information reported to FDA involving self-monitoring blood glucose systems. First, I will provide a brief overview of the reports received by

the Agency from 1984 to the present and then I will present information summarized from recent reports received during the calendar years 1995 and 1996 in order to focus on currently reported device-related concerns.

FDA's mandatory device reporting program for manufacturers began in 1984. Since that time, self-monitoring blood glucose systems have been the product line most frequently reported within the in vitro diagnostic product area. Between 1984 and 1997, an average of 684 self-monitoring blood glucose system reports had been received per year in comparison to an average of 883 reports per year for all other categories combined of in vitro diagnostic products.

Notice the first arrow on the left of the graph, marking a change in the in vitro diagnostic device report patterns beginning in 1992. The enactment of the Safe Medical Devices Act in the 1992 Medical Device Amendment was expected to increase the number of adverse event reports received by FDA, which appears to be the case with in vitro diagnostic devices as a whole, beginning in 1992.

Now, notice the second arrow to the right of the graph. Beginning in 1993, the curves began to diverge. By 1994, it appears that the self-monitoring blood glucose

meter reports had peaked and begun to taper off and are no longer tracking all other in vitro diagnostic device reports as they did in the past.

Why is this? Well, there are a number of factors related to the enactment of SMDA that affected historical reporting patterns for medical devices during this time period. However, beginning in 1995, FDA began to grant a new type of MDR reporting exemption to requesting firms for instances when a manufacturer had initiated a voluntary recall to address a recognized device problem. We believe that the recent divergence in historical reporting patterns between self-monitoring blood glucose systems and other in vitro diagnostic device lines is, in part, due to the granting of such reporting exemptions.

From 1984 to the present, a total of 22,425 adverse event reports have been submitted to the Agency for problems associated with the use of in vitro diagnostic products. Within the IVD product area, self-monitoring blood glucose systems are the most frequently reported product line. To date, they account for 7,425 or 33 percent of all adverse events reported to FDA involving in vitro diagnostic products.

Blood glucose meters are literally used millions

of times daily and hundreds of millions of times yearly, it has been estimated, and the number of reported adverse events are very small numerically when compared to the number of annual uses of these systems. However, recognizing the limitations of our reporting system, FDA considers the reporting patterns for blood glucose monitor systems to be noteworthy.

Self-monitoring blood glucose meters are the IVD category most frequently associated with reports of death, serious injury and with malfunctions that could cause death or serious injury if they were to recur. They account for 48 percent of all IVD-related death reports, 59 percent of IVD-related serious injury reports, 36 percent of malfunction reports for in vitro diagnostic devices and 8.4 percent of IVD-related reports that were coded as "other" in our system.

Because the market has changed and the use of these devices has significantly expanded over the last ten years, we wanted to examine information in the more recent information reported to FDA during the previous two calendar years. During 1995 and 1996, blood glucose monitoring systems remained the most frequently reported problem category of in vitro diagnostic products, accounting for 27

percent of all reported in vitro problems.

Within this time frame, they also continued to be the in vitro diagnostic product line most frequently reported in association with death, serious injury and malfunctions that could cause death or serious injury if they were to recur.

To better understand the nature of the reported information involving blood glucose monitor systems, we manually reviewed and subjectively scored a representative sample of 1,310 reports received during 1995 and 1996. For each report, we determined when possible who first appeared to recognize that there was a device problem, which system component reportedly malfunctioned and caused inaccurate meter readings. And I wanted to note that for the purpose of this exercise, we considered the user to be a component of the system.

We determined when possible how the device failure or malfunction reportedly affected the meter readings, what type of clinical consequences were experienced by the patient as a result of the alleged failure or malfunction of the device and we attempted to determine and quantify the magnitude of measurement differences from the user's perspective that were reportedly observed either between

sequential meter readings on the same system or between meter readings on different brands of meters or laboratory systems that from the user's perspective, quote, should have been the same.

In the reports sampled, the patient appeared to be the first to recognize the alleged device problem 71 percent of the time. Seven percent of the time the device problem appeared to be first recognized by a family member or a caretaker. Seven percent of the time the problems were first recognized by the patient's health care provider and in 15 percent of the reports, we were unable to determine this information.

It is important to note that in many cases the reported device problems were recognized only after significant clinical consequences had been experienced by the patient.

Sampled reports indicated that the test strips were the problem component in 51 percent of the reports.

User error was indicated as the primary cause of the alleged device failure in 20 percent of the reports; the meter itself in 17 percent. The control solution related issues accounted for 1 percent of the reports and in 11 percent of these reports, we were unable to determine this information.

In a number of cases where the test strip or monitor problems were reported to have caused the device failure, the reports also suggested that recognition of the device failure or malfunction was obscured when the device user failed to perform recommended quality control checks or otherwise maintain the system.

In some cases, device problems originally attributed to user error were subsequently found to have been caused by device defects.

The sampled reports indicated that the device malfunction resulted in false low readings 43 percent of the time; false high readings, 28 percent of the time. There were erratic results reported in 4 percent of the sample and out of range controls with test strips were occurring according to these reports in 16 percent of the time.

In 9 percent of the sampled reports we were unable to determine this information.

Thirty-two percent of this sample set of events in the report text indicated that there was a range of serious clinical consequences, including death, that were attributed to the failure of the device. But this information was not in most of the reports and in 68 percent, we were unable to determine this. But I wanted to note that in that subset of

68 percent of the reports, you will see a heading "CR by Manufacturer" and "CNR by Manufacturer." That stands for "counseled and referred" and "counseled and not referred."

What that means is that information provided in some reports appeared to indicate that the only contact the user had regarding the reported event was with a device manufacturer via telephone. In some cases, the reports indicated that the manufacturer's representatives requested that the user conduct multiple measurements during phone conversations, either by lancing themselves and/or by using various control solutions and test strips.

In some cases, these reports indicate that the callers were referred to their health care provider for further assistance. In other cases, even when there appeared to be a device problem, the reports do not indicate whether or not the device user was advised to see their physicians regarding their performance concerns.

As I previously mentioned, we attempted to determine, based on information contained in adverse event reports submitted during the calendar years 1995 and 1996 what magnitude of measurement differences from the user perspective were observed between meter readings on the same or different systems that, quote, should have been the same.

Why did we do this? Well, it appears that the differences in measured values obtained on the same blood glucose meter or using different blood glucose meter systems or laboratory systems when discovered by the user constitute the point in time at which device users become aware of potential device-related problems.

This awareness appears to be the motivation for the user to report their device-related concerns to the manufacturer, their health care professional or to FDA.

Only 418 of the 1,310 reports that we sampled supplied enough information that allowed us to calculate the percent difference in blood glucose system measurements reported by the users. The percent difference calculation that we used is a relative measure. It assumes the lowest of the two measured values to be 100 percent and there is no assumption of the correctness of one measurement over the other.

What was the percent difference? Well, based on these sample reports, using information regarding back-to-back measurements or measured values that appeared to have occurred during a reasonable time period, we found the percent differences to range between 6.5 percent and 13,567 percent, with the average percent being 438 percent.

What does this average percent difference number actually mean? Well, it means that on the average for this subset of 418 sampled reports, when either back-to-back readings or readings were made within relatively short time frames, using either the same or different systems and those measurements should have been, quote, the same, the difference between the two measured values was on the average, 4.4 times the lower of the two measured values.

I would like to summarize as follows: FDA is not certain what these observations mean in terms of the real world of patient use, but with respect to the reported information, we observed that there were no big surprises. The reported device problems appear consistent with the recent system performance concerns expressed in the medical literature that were summarized by Dr. Gutman in his earlier presentation.

Self-monitoring blood glucose systems continue to be the in vitro diagnostic product line most frequently reported in association with death, serious injury and device malfunction reports. We note that these devices are used millions of times daily and the reported number of device-related events is guite small.

However, recognizing the limitations of our

reporting system, FDA considers the skew in the reporting patterns for in vitro diagnostic products toward blood glucose monitor systems to be noteworthy. Test strips were the most frequently reported system component allegedly associated with failures or malfunctions of these devices.

We know from information provided by device manufacturers and FDA postmarket follow-up efforts that some groups have reported problems originally attributed to user error were subsequently determined to be caused by device defects. We know that many of the reports indicate that recognition of a device problem was most likely delayed or obscured when device users did not properly clean and maintain their systems or perform manufacturer recommended quality control procedures.

Mr. Chairman, members of the panel, we hope this information proves useful to you as you consider the complicated and important issues at hand. I personally would like to thank everyone for their attention and let you know that I will be available later in the program to answer any questions that you may have.

Thank you.

DR. NIPPER: Thank you very much.

Ms. Dillard, we will, in open committee

discussion, after Ms. Rooks has presented, I am sure we will have questions for you. Thank you.

Our next speaker is Cornelia B. Rooks, who formerly was the executive secretary of this group. We plan to be ruthless and show no mercy. She is currently the director of the Division of User Programs and Systems Analysis, Office of Health Industry Programs, Center for Devices and Radiological Health.

I have been instructed by the executive secretary to use the acronym DUPSA when describing where Cornelia works.

Agenda Item: FDA Presentation -- Premarket Review Guidance

MS. ROOKS: Thank you very much.

Good afternoon to our distinguished panel members and guests.

It is my pleasure to greet you this afternoon from this side of the table. I do have to admit it is a bit intimidating from this vantage point.

As Dr. Nipper has stated, my term as exec sec has ended and I would like to welcome Ms. Sharon Lappalainen, my most capable successor. And I also would like to welcome Dr. Nipper as the new chairperson. You both are doing a

commendable job.

It is my task today to discuss an FDA document currently entitled "Review Criteria for Assessment of Portable Blood Glucose Monitoring In Vitro Diagnostic Devices, Using Glucose Oxidase Dehydrogenase or Hexokinase Methodology."

This document is dated February 14, 1996, and has been provided in your folder and it is currently available to the public through DISMA(?) by fax on demand and on the Internet.

Before I discuss the guidances, I would like to briefly give a definition and use of guidance documents. Guidance documents have been issued under a number of different names; for example, guidelines, guidances, points to consider, review criteria, et cetera. In order to eliminate confusion regarding our guidance process, the Agency published a request for comment on the development and use of guidances on March 7, 1996. Subsequently, the Agency published -- I am sorry -- a request for comment on March 7, 1996. Subsequently, the Agency published a Federal Register notice dated February 27, 1997, entitled "FDA's Development, Issuance and Use of Guidance Documents, Good Guidance Practices."

In this document, guidances are to (1) provide assistance to regulated industry by clarifying requirements that have been imposed by Congress or issued in the regulations by FDA and by explaining how industry may comply with those statutory and regulatory requirements and (2) provide specific review and enforcement approaches to help ensure that FDA's employees implement the Agency's mandate in an effective, fair and consistent manner.

These documents include documents prepared for FDA staff, applicants or sponsors and the public, relate to processing, content and evaluation or approval of submissions; (2) relate to the design, production, manufacturing and testing of regulated products; (3) describe the Agency's policy and regulatory approach to an issue and (4) establish inspection and enforcement policies and procedures.

Guidances represent the Agency's current thinking on a subject; in this case, glucose testing. Guidances that are not special control do not bind the Agency and they do not create or confer any rights for or on any particular person. While the issues or questions raised in guidances must be dealt with by sponsors, the specific suggestions provided for addressing these in guidance are suggestions

only and can be addressed using alternative mechanisms, providing these are scientifically and statistically correct.

Based on review experience and the emerging scientific literature, evaluating self-monitoring blood glucose devices in both idealized and real world settings, FDA first developed a guidance document to assist in reviewing glucose meters and strips in 1991. This original guidance was subsequently revised in February 1996.

Over the past year, comments have been received from both the manufacturing community and from members of the Division of Clinical Laboratory Devices, suggesting ways in which the document can further be improved, as well as revised according to the good guidance practices document.

The current definition of the products that are addressed in the guidance document is "Portable blood glucose devices are intended for use in hospitals, at point of care, in physician's offices and over the counter as in vitro diagnostic tests for the quantitative and semiquantitative measure of glucose by glucose oxidase, dehydrogenase or hexokinase-based methodologies."

These do not include the larger clinical chemistry analyzers or the dedicated glucose analyzers used to perform

routine and stat glucose testing on plasma, serum, urine and cerebral spinal fluid.

Please keep in mind that the same device could be used in all the settings that were previously described and used by professionals, as well as lay persons.

Glucose test systems are Class II devises regulated as 510(k)s. The regulation can be found at 21 CFR 862.1345. The existing guidance is a document, which provides current thinking on how to prepare submissions to obtain expedient Agency clearance. It provides suggestions on the studies needed to establish performance for this type of device, a discussion of human factors issues to be considered in the design of the device and some labeling guidance.

As Dr. Gutman has previously stated, other guidances are available for labeling and over-the-counter products. This document itself also references several NCCLS voluntary standards, which may be of use as a manufacturer defines product performance.

While the current document does recommend NCCLS or equivalent in general for acceptable performance testing as precision, linearity, interference, bias and method comparison, it falls short in recommending specifics for

glucose testing. There is no information on possible performance goals; for example, for key analytical parameters, such as bias, imprecision or total error.

There are no mandatory performance standards or generally accepted voluntary standards for glucose testing. We are interested in any and all improvements which can be made to the guidance document, but, in particular, as Dr. Gutman stated earlier, we are seeking input on two sections, which could perhaps be improved to provide specific recommendations.

For example, in Section 4, should FDA encourage use of specific reference methodology to trace analysis? Should FDA make recommendations for a specific number of meters, lots or for more variable testing environments to obtain a more global perspective on probable device performance? Or should FDA suggest goals for total error to components of error?

In Section 5, should FDA provide simple but more detailed description about the device's performance in the package insert or the device labeling? For example, should FDA specifically suggest precision, bias and total error be outlined in lay terms and compared to any particular set of standards or parameters?

In addition to these recommendations, can FDA contribute in any manner through labeling or other review of regulatory practices to the improved use of quality control in the home test use arena?

While FDA is seeking input during this panel meeting and in the post-panel period for how to improve our existing guidance, we are also seeking input on whether alternative mechanisms of review direction are appropriate to improve performance in this area.

In addition to guidance documents, other mechanisms for communicating review direction are voluntary standards or consensus, performance standards and regulations. One mechanism for providing direction for FDA review is through use of voluntary or consensus, national or international standards. For in vitro diagnostic products, the national standards group that has been most helpful in directing review is NCCLS, which has an extensive series of documents to assist in establishing performance characteristics for a variety of tests.

NCCLS to date has been very active in defining evaluative techniques or methodologies but has not attempted to define minimal levels of analytical or clinical performance for lab tests. FDA can recommend that

manufacturers consider use of NCCLS techniques or standards, but cannot require these unless designated as special controls. More about this later.

FDA is aware that other guidances exist, including the Canadian standard on glucose systems. Additionally, the Agency is currently participating in the ongoing effort by the ISO-212 International Standards Committee to use the Canadian standard as a nidus on which to establish an international standard for evaluating these devices.

Voluntary standards are appealing to the Agency because they involve interaction by all stakeholders; industry, government and professional groups. And as a result, the voluntary standards practice tends to result in a balanced and well thought out document.

A second mechanism for communicating review direction is through the use of performance standards. The performance standards are promulgated in accordance with Section 514(a) of the Federal Food, Drug and Cosmetic Act. The performance standards for a device is intended to include provisions that provide reasonable assurance of its safe and effective performance.

The provisions can include construction, components, ingredients and properties and its compatibility

and connections to power systems; provisions for testing the device, provisions for measurement of the performance characteristics of the device, provisions requiring that the results conform to the standard and provisions requiring that the sale and distribution of the device be restricted under 520(e).

The performance standard, where appropriate, can require the use and prescribe the form and content of labeling for the proper installation, maintenance and operation and use of the device.

Mandatory performance standards require rulemaking and are binding. Their development can be accomplished by interaction between FDA and industry through formal mechanisms, workshops or informal working groups.

These are published only after there has been a formal opportunity for public comment. One way to better define minimal performance or labeling for glucose meters would be through an Agency/industry interactive process to develop formal performance standards.

The most stringent mechanism for communicating review direction is through the regulations promulgated by the Agency to interpret the law. While these regulations, which are published as part of the government's Code of

Federal Regulations, are, of course, always subject to variant interpretations, they are intended to provide definitive definitions, explanations and policies to guide FDA review.

Regulations are developed according to a formalized process, which allows for formal outside input and provides the Agency an opportunity to develop regulatory changes in the context of this input. Examples of regulations are the glucose test systems reg, stated previously at 21 CFR 862.1345, and the labeling regs in 21 CFR 809.10.

The mechanisms for communicating review direction that I presented previously, guidances, voluntary standards and performance standards, can, in fact, be designated as special controls. The Safe Medical Device Amendments of 1990 redefined Class II devices, such as glucose test systems, as those products for which special controls are adequate to provide reasonable assurance of safety and effectiveness.

Special controls are defined by statute as those controls, such as performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, including guidelines for the

submission of clinical data and premarket notification submissions in accordance with Section 510(k), recommendations and other appropriate actions, for example, labeling, that provide reasonable assurance of the device's safety and effectiveness that cannot be provided by general controls.

Special controls should be selected that adequately address the risks posed by the device. In making the decision on which special controls are applicable, one must ask what are the risks posed by the device and can those risks be adequately managed through application of guidance, standards, enhanced labeling or any other special control.

Special controls, however, require rulemaking and are binding.

I have just presented a brief overview of the mechanisms available to provide direction for review of medical devises, such as self-monitoring blood glucose systems. During the course of the next day, we hope to stimulate and generate discussions that help in the revision of the guidance document, as well as discussion on alternative mechanisms, which will allow continuous improvement of self-monitoring blood glucose devices.

Thank you very much for your attention and I will be available to answer any questions that you may have.

DR. NIPPER: Thank you very much, Ms. Rooks.

Agenda Item: Open Committee Discussion

At this point, I am wondering if the panel has any particular questions for either of our presenters, Ms.

Dillard or Ms. Rooks.

Dr. Kurt.

DR. KURT: Yes. At the time that Ms. Dillard showed the chart showing the number of reports per year, she described that after the 1990 device law was passed, that there was a difference in the reporting rate, due to exemptions that were granted.

What were the exemptions that were granted?

MS. DILLARD: Let me be clear about that.

There were changes in the 1990 Safe Medical

Devices Act in terms of reporting and for the first time,

device distributors and user facilities were now required to

report certain types of events and certain circumstances.

So, at the time that was passed, because manufacturers were

the only group subject -- device manufacturers -- subject to

mandatory reporting requirements, it was thought and, in

fact, it has come to pass that the enactment of that law

would increase reports to FDA for medical device problems, which if you look at that graph, you can see clearly that they go up in both the glucose and other in vitros.

What I meant to say and what I hope I was clear about is if you look around 1993 on that graph, you will see --

DR. KURT: There is a pall at that point.

MS. DILLARD: Well, there is a peak and then a fall off. Let me grab this for you. From memory here, at first after 1992, the curve goes up and keeps pretty much in line with the other in vitros. Then you will see a peak and then it drops off.

When it peaks and begins to drop off, what happened is that under these new authorities, there was an option for FDA as an encouragement for manufacturers to take timely and appropriate action to correct recognized device defects, a reporting exemption. And the thought behind those types -- it is called a remedial action reporting exemption and the thought was that for device problems that had been recognized and acted upon by the manufacturer and had had a classified recall action by FDA, based on their voluntary action, that there was no need to report anymore events of that type because our system at that point had

done everything that it needed to do because we had reports that the problem was recognized and action was taken to correct it. So, further reports would seem to be unnecessary to -- and it was an incentive.

So, what happened is we know that we did grant some of these for in vitro diagnostic device manufacturers and for glucose meter and strip manufacturers and that, we believe, in part, played a role in that dropoff and without the exemptions, that curve probably would have climbed and looked a little differently, at least the red part of the curve.

DR. KURT: Could you characterize any of the exemptions that occurred at that time?

MS. DILLARD: I really didn't come prepared to do that and I will tell you why. Of all the graphs that I presented today, the point that I wanted to make with this is that this isn't a new problem. What we are seeing with blood glucose meters has been going on for a long time. This is not a new unusual emerging issue. It is an issue that has been marching along for some time.

One of the hopes that I had for my presentation was to show that the problems that we have received in terms of the event reports are, indeed, the generic types of

problems that the speakers today that came up, talked about, that the medical literature references and that, in fact, I wanted to divert it away from particular manufacture-related issues and make it a more generic issue.

That information is available, though, under Freedom of Information. I can provide it to the panel upon request at a later point in time and I would be happy to do so.

DR. NIPPER: Is it your point that the problems we are seeing with these devices then are generic and a large number of them are user-related? Is that the point or did I miss it, too? Did I miss it period?

MS. DILLARD: Well, my point is that you really can't make that kind of inference from this information. It is what it is. There are limitations in terms of the reports, based on the reported practices of the manufacturers, based on the use of the voluntary system and so forth. So, I can tell you what is reported, but I can't really tell you what that means in terms of the real world.

That is one of the reasons, I think, we are all here at the table today, to try to understand better what these sorts of things do mean.

DR. GUTMAN: Let me add a couple of points to that

because I am a partner in crime in having not analyzed the data personally, but watching as Sharon has done a fabulous job of trying to analyze a very difficult data set.

There are a couple of observations that I can make and one is that whatever is going on here is going on in the context of what we think is steadily increasing use of the product. So, we don't really know probably either the numerator or the denominator, but we think the ratio is staying the same or getting better and better because I think there is more and more of the product use now than there was ten years ago.

The second thing that struck us from the start and one of the reasons we have this panel meeting cast in sort of general terms and we don't have delusions of grandeur, we see it as a starting point, rather than some two day quick fix, is that the complexity of this problem is overwhelming actually and that we can talk about the review part of it and maybe tomorrow the manufacturers will talk about the manufacturing part of it.

There will probably be a user part of it and there is probably going to be an educational quality control part of it. It is just really, really complex and we would be looking for this as a starting point maybe for a series of

other initiatives that might improve various aspects of a complex problem or it might be that you don't think it is a problem. Maybe we should not be doing a lot more, doing a little bit of refinement of where we are right now and watching as the new technology breaks through.

We are also looking -- have already had some discussion -- there was some interesting discussion in the comment period before about being proactive as the technology changes or as the new technology comes along, can you give us any hints or help or can you give the industry any hints or help on how we can all do a better job at getting this stuff faster.

So, there are all kinds of levels. It is a very rich issue and we didn't really expect Sharon, using the less than clinical trial database to be able to give you really definitive answers.

DR. NIPPER: Okay. Thank you.

Yes, Dr. Zawadzki.

DR. ZAWADZKI: I would like to ask a point of clarification regarding the slide that showed reported failure mode, meter readings. That is SMBG's adverse event report.

MS. DILLARD: Would you like us to put that back

up?

DR. ZAWADZKI: Sure.

MS. DILLARD: Okay.

DR. ZAWADZKI: Actually, my question is a simple one. The majority of these adverse events are related to a falsely low or falsely high glucose reading. How is that determined?

MS. DILLARD: The only determinations that we could make were when information was provided in the report and the events are typically reported by the manufacturers and the reports from the manufacturing community I wanted to say constitute the prevalent reporting group and a very small number have been submitted in comparison by voluntary reporters or by user facilities.

When that information is provided to us, the report states that the measurement was a false high or a false low. And if it did not state it, which it did not in 9 percent of the cases, we were unable to determine that. So, this assessment is based on the information as it was reported to FDA.

So, for example, if the event text read "The readings were confirmed to be false low and the device failed in a way that caused the user to be hospitalized,"

well, what we said was that was a false low reading.

I hope that helps. This is very -- it is hard to explain. I wish I had had a report for you to look at, so you could see what we did and we had to manually read everyone of these reports to get this information. They are not coded fields.

So, we did that to try to get a feel for what we were seeing.

DR. ZAWADZKI: I just want to clarify if this is subjective or an objective report. Are they comparing this to simultaneous laboratory method or is this an impression that somebody -- that some reading was high or low and, therefore, an adverse event occurred?

MS. DILLARD: It could be both. It could be any or or and sometimes the reports say -- that is why it is important to understand that and how soft -- I don't even like to say the word -- but how "soft" this information really is because we only have what we have.

What happened in some of the cases was that the patient required emergency treatment, was taken to the hospital. Someone had their meter and stuck them with the meter they had been using at the hospital and the meter read 20. When they did the hospital level, the blood glucose --

and these are true situations -- read 1100 or greater and the reporter said that this was a false low reading.

So, in some cases that is the way it was determined; in some cases it was based on symptomatology, it appears to us, but there is quite a range. So, it could be any or all.

DR. ZAWADZKI: Thank you very much.

MS. DILLARD: You are very welcome.

DR. NIPPER: I am almost speechless at that last one. That is accomplishing something for me.

Are there any other questions to be raised for either Ms. Rooks or Ms. Dillard by the panel?

Dr. Cooper, I know you have to leave early, so -- Dr. Rej?

DR. REJ: Just a couple points of clarification on the database.

You refer to them as self-monitoring blood glucose systems. Included in this database would be professional use, rather than self-monitoring use? In other words, if they are being used in a hospital.

MS. DILLARD: No. They were all self-monitoring systems and even though I think primarily they were intended for home use, they are used at the bedside quite often and

it included both bedside use, as well as home use, of these types of over-the-counter product.

DR. REJ: So, an event in a professional setting was included in your database?

MS. DILLARD: Correct, if it involved these types of products.

DR. REJ: It was the type of the device rather than the self-monitoring part of it?

MS. DILLARD: Correct.

DR. REJ: Okay.

Just for clarification on the non-blood glucose systems, were any other over-the-counter type systems included in that, pregnancy test and so on?

MS. DILLARD: Yes, they were included and that was any other report aside from self-monitoring blood glucose systems, as we refer to them.

DR. NIPPER: Okay. Let me just reiterate something Dr. Rej said. These -- and this is important because I think several of us around the panel are confused about -- and maybe people in the audience also -- are confused about getting a handle on how these devices are used. If their major intent is to help a diabetic patient monitor their home -- their situation at home and the data

you have got is all home -- is all lay use in self-monitoring --

MS. DILLARD: No. It --

DR. NIPPER: -- then that tells us one thing. If it is also including the 12,000 dip sticks a month that are done at St. Joe Hospital in Omaha at the bedside by technicians of people who are acutely ill and that gets mixed in as well and the differences between false high and false low are gauged against the laboratory glucose analyzer, which is checked everyday, then that gives you a lot of data to -- because I am thinking that that data may be skewed -- that this data may be skewed because the professionals tend to be a lot harder on these machines and expect more of them and complain when they don't work.

Maybe I am wrong about that, but it seems like to me that that would contaminate the database if we are thinking about home use of glucose monitors.

DR. ROSENBLOOM: But aren't these adverse events?

They are not just machine failures. Don't they have to be adverse events?

MS. DILLARD: Correct.

DR. ROSENBLOOM: Yes. So, it is when something bad happens.

DR. HARRINGTON FALLS: But all of these reports are anecdotal. They are self-reported and so there is no secure database.

MS. DILLARD: Let me be clear. It is a complicated issue and just so you don't feel uncomfortable not understanding, sometimes there are things I don't understand. Our normal talk to explain our reporting system takes a day. I had ten minutes.

So, there are a lot of subtleties that I am not going to be able to communicate to you in ten minutes. But what I wanted to communicate is in light of those subtleties -- and we are aware of all of them -- we used the database responsibly.

what I want to tell you if this helps you understand is that all the reports that were included in that slide of the pie under self-monitoring blood glucose systems were actually meter systems and that is it. There are very few reports in our system -- in vitro diagnostic systems are not frequently reported for a number of reasons. And, again, I think that goes beyond the scope of our discussion today.

But very rarely have we -- I think maybe a handful of complaints on dip stick-related problems in our whole

system. Those were included in all other in vitro products because for the point of my talk today, I was asked to deal specifically with the meter systems.

DR. NIPPER: I am sorry. I used the word "dip stick" but that shows you how old I am. I meant a stick that you put something on and shoved into a meter.

MS. DILLARD: Ah. That includes -- those are included in the other side then. The semantics of these issues are also daunting.

DR. NIPPER: Yes. Well, especially when I started out with dip stick stuff.

MS. DILLARD: I think of those as test strips.

DR. NIPPER: My frustration, you know, and it is very mild frustration, is that I am looking for the handle on this stuff that you have told us about and I am particularly interested in it in light of meeting Goal No. 2, which actually we could put up on the screen, to think about goals that are appropriate for different groups of patients and different treatment regimens.

So, you see, if we have got problems that are in this adverse events and the adverse events are coming from different groups of patients and different treatment regimens, it would be wonderful if we could know that. If

all of these things were self-monitoring blood glucose adverse events, then that helps us a little more. You see what I mean?

MS. DILLARD: Yes, sir. And I think I can help you.

None of those in the slice of pie were from professional use systems and, in fact, again, for those systems that you are talking about, the benchmark lab systems, clinical lab systems --

DR. NIPPER: I am assuming they are not ectokins(?) and STAs(?). I am assuming that they are little meters that are up on the floors that are being used at the bedside by whoever tends to do that dip stick on the ward.

MS. DILLARD: Right.

DR. NIPPER: Okay? At the point of care testing in clinics, bedside testing, as described by the College of American Pathologists' speaker, Dr. Ross -- I am assuming that that is into the vegetable soup.

MS. DILLARD: It would be in the soup if there were any reports, but there really aren't any. I mean, the reports that we have that I summarized for you, I looked at specific Pro Codes and those are Pro Codes for the meter strips system combinations that are used in the over-the-

counter setting.

DR. NIPPER: Okay.

MS. DILLARD: And there are reports in our system, a few, for the meter systems, but very few, and they were included in that "other" group. But I mean there is like maybe -- I hate to say because I don't have the number, but I assure you that it is somewhere less than 10 a year, if that many.

DR. NIPPER: So, these are the diabetes patients' problems?

MS. DILLARD: Yes, sir.

DR. NIPPER: Okay.

MS. DILLARD: I am sorry that I wasn't more clear on that.

DR. HABIG: I am not yet clear because I think I have now heard you say two different things. My definition of this would be reports on any meters cleared specifically by the FDA for home use regardless of where they were used.

MS. DILLARD: Yes.

DR. HABIG: So, a meter cleared for home use, many of which are on hospital nursing station places could be in these reports.

MS. DILLARD: They are.

DR. NIPPER: That is what I kept asking.

DR. HABIG: We all thought you just said --

MS. DILLARD: I am sorry.

DR. HABIG: So, these are any meter that is cleared for home use, which when used in the home is by the CLIA classification a waived meter by definition.

MS. DILLARD: Right.

DR. HABIG: Many of them are on hospital nursing stations.

MS. DILLARD: Yes.

DR. HABIG: And are used by nurses and other health care professionals and when they see a problem, they make a report.

MS. DILLARD: Yes.

DR. HABIG: Those reports are in this 35 percent.

MS. DILLARD: 33 --

DR. HABIG: Okay. 33 percent.

MS. DILLARD: Yes, they are but they are very -they constitute a very, very small portion but whatever we
had we did include in that.

DR. HABIG: Okay.

And it is my belief that the -- saying that they are a small percentage of the total reports is actually

useful as well, because what I said earlier about expectations, even of health care professionals of the kind of cleared for home use meter used in a nursing stations, the expectations are generally that these things ought to match the laboratory and that a report would come pretty frequently about they didn't match the laboratory.

As I said earlier, they were neither designed nor are they labeled to match the laboratory and, in fact, they are not standardized to match the laboratory. Its capillary whole blood. It is not a venepuncture on a plasma analyzer, et cetera.

It would be really good to know if you know or if the database could tell you a quantitative number. You said a small number. Is there a way to dig that out between now and tomorrow morning? Because I think it would be useful to know. It might shed some light on the seriousness of the issue relative to use in a health care setting.

DR. NIPPER: Okay.

I will call on you next, Dr. Boughman.

I just wondered if you had a response to Dr. Habig.

MS. DILLARD: I want to tell you two things very quickly. One is that we are limited by the information in

the reports and there were a few -- and, again, I didn't -there were several people who scored these for different
criteria. So, I can only tell you that my overview and my
impression of the quite a large number of these that I
personally scored was that I saw one or two reports that
originated in a hospital setting.

Well, in terms of our reporting system, why would this be? Well, I think someone on the panel already pointed out, well, these are adverse incidents and because a device that fails or malfunctions in a home use setting for whatever reason, depending on a number of factors, it is probably more likely to result in serious adverse consequences under certain circumstances than one used in the hospital, where you have the benefit of care givers making observations and quick corrective actions and so forth.

So, there may be a skew in the reporting in that direction. And malfunction reports are not frequently submitted from the hospital settings for a number of reasons because they typically presume that they would catch these types of problems, then it wouldn't cause or contribute to a death or serious injury.

So, there are determinations like that made. But

the best I can do to answer your question, I think, within the time frames we have is to point out that in terms of who recognized a problem with a device, 7 percent were recognized by health care professionals and that included in those 7 percent both problems that were recognized in a clinical setting, as well as problems that when patients went in for routine care and they did a meter test at the physician's office and then a meter check was made, at that point the meter called patient and said, gee, you know, you have a problem with your meter.

So, in total, of the reports we saw, 7 percent were recognized by health care professionals. I hope that helps a little bit.

DR. NIPPER: It does.

Dr. Boughman is champing at the bit.

DR. BOUGHMAN: She actually made the point before I had a chance to with the possibility of intervention before the adverse event became a full-blown adverse event in a hospital setting under the watchful care of the health professionals.

DR. NIPPER: And what that does is scare the hell out of everybody and waste time and money if it is not an adverse event.

DR. BOUGHMAN: Right. That is right. At least it does not become a reportable adverse event.

DR. NIPPER: But it is still a problem.

DR. BOUGHMAN: Absolutely.

I would ask a very different kind of question and I am going to try and make this as clear a question as I Rather than focusing on percentages or whatever, given the database, one of those problems, though, that seems to have some magnitude to it is related to the test strips and this question and issue becomes very complex very quickly, given some of the comments by the speaker from the ADA and I think Dr. Ratner's comments as well, that the use of test strips or the abuse of test strips and/or use of test strips in a different context or with a different meter than they were manufactured to go with -- there are lots of different combinations and the question that I really have is, not having been through an actual review of one of these devices that we are referring to right now -- during that review process, are the test strips and the meters looked at differently or only the combination of the two together in any of the precision tests or whatever? Is there ever any process that separates the two to look at potential errors?

MS. DILLARD: I would like to defer that question

to Dr. Gutman because his group is responsible for the premarket review of these types of products.

DR. GUTMAN: I am sorry. You will have to repeat the question.

DR. BOUGHMAN: Given the data presented this afternoon and that the test strip seems to be the origin of a large proportion, whatever that exact percentage is -- I think it was reported to be 51, but in the premarket analysis, is there the process by which the meter and the strip might be looked at for accuracy, precision, all of these events separately or are they considered only as a unit during the premarket or any postmarketing studies?

DR. GUTMAN: We look at the products, frankly, as a unit and I don't know if we -- certainly, as you see that information, you have the capacity to break down into various error components, but as you can see from looking at the document, it is -- at least in terms of being either proscriptive or even in terms of providing recommendations or guidance, not very direct if it doesn't suggest a certain number of meters, it doesn't suggest a certain number of strips, it doesn't suggest or specify that you must clearly at decision points look at bias and precision and total error.

It is certainly my belief that as we look at these, we are looking at those in a global sense and I guess our challenge to you is to tell us and tell the manufacturers whether that is good enough or whether there ought to be a more refined or more sophisticated approach.

You can't generalize because different manufacturers with different submissions will come in with very different data sets. So, it is a question of where we set our minimum standard.

DR. BOUGHMAN: The interesting part of this is that we are coming at the entire issue this afternoon in a very different way than we would have if we were presented with a 510(k) from a manufacturer that presented us with a package. What we are being asked to do now is, in fact, from the user perspective essentially and all of the different combinations of errors that I could produce as a user now ask the question what can we ask of the manufacturers and in labeling or otherwise. And that really is a very different perspective, but I think that this is one point we may want to spend some time at least thinking about individually, about looking at these data in such a way either in premarket approval or in postmarket testing, especially with the possibility of even generic strips

coming out that purportedly can be used with one or more devices.

So that we, in fact, are protecting from that very large error bar, contributing to these adverse events.

DR. NIPPER: Thank you.

Dr. Rej.

DR. REJ: I have a comment and a question.

That 51 percent for the strips really stood out on that slide, but I caution a little bit in that when you have one aberrant result, just something that is out of line, you repeat it and everything seems fine. It seems fine with the clinical situation. It is very tempting to say, oh, it was the strip because it is consumed. There is no way to check it out.

Usually we have one flier like that. That is a convenient catchall but it may not be correct. So that column may be a little bit exaggerated. Would you agree with that as a possibility?

MS. DILLARD: I think anything is possible.

Again, I don't know how to translate this to reality, but --

DR. REJ: If it were me reporting it and there was this one flier and there was nothing else, I would say, oh, it was a lousy strip because it is convenient. It is a very

convenient scapegoat.

DR. NIPPER: Especially if you are a lay person.

DR. REJ: Yes.

MS. DILLARD: I agree.

DR. REJ: Well, even as a professional.

MS. DILLARD: I agree and in my talk I also pointed out that originally some of the problems that begin to crop up with devices that were originally reported as use error turned out to be actually be device problems of different types. That is important to know, too.

So, the skew in this may not reflect reality but it, at least, reflects the point that motivated the reporting to FDA.

DR. REJ: That is clear.

Henry, I have one question probably best directed at Dr. Gutman or maybe Ms. Rooks.

Earlier I talked about a professional use product being used by a consumer, not necessarily legally, but these devices, as I understand it are cleared for home -- over-the-counter home use. Correct?

DR. GUTMAN: That is correct.

DR. REJ: Is there any problem with using these in a professional setting?

DR. GUTMAN: Well, that is a very interesting question. We cleared these as over-the-counter devices. We try to label them for what they are. We want to talk tomorrow or have you talk to us about whether our labeling ought to be improved, but we try to label them for what they are and the way our regulatory framework interacts with the clear regulatory framework is that by default an over-the-counter product is considered automatically waived.

There are two different points of views that have been passionately discussed in a number of CLIAC(?) meetings in the past and one is, well, of course, if your mother-in-law can run it, then, of course, the doctor can run it also. It is not rocket science. It is something you can buy at K-Mart or Wal-Mart. The doctor ought to be able to run as well. That is one point of view. That is the prevalent point of view at this point and that is the way the two statutes interact.

The alternative point of view is, gee, I would expect to get a slightly better result when I go to Dr. X than when I do it or when my mother-in-law does it in my own basement and there really ought to be different standards in different settings. The best we can do is try and address this through labeling because of the constraints of the two

statutes.

DR. REJ: I think that is very germane to the questions posed to the panel because what are the requirements of the systems. So, there is some possibility that the professional use of these over-the-counter products in a hospital settings --

DR. GUTMAN: It is quite legal and there is a certain tension between our statute, what we were talking about this morning when Pat was talking about our concerns about the product this morning, is that we are looking at equivalency and safe and effective -- substantially equivalent and as safe and as effective and we allow -- we may allow a lot of interaction in a particular determination.

The statute that -- the operation from which the CLIA is basing its Wade decision is a standard based and they allow, I would say, essentially no statistical error before they would allow something to be weighed and there is a tension between those two regulatory processes that the two agencies continue to try and adapt to.

DR. REJ: Thank you.

DR. NIPPER: Thank you.

I share some of the same concerns that Dr. Rej is

articulating.

Dr. Cooper.

DR. COOPER: The last few minutes have been helpful in crystallizing the difference in its applications. Before that, though, there was some discussion -- I think Dr. Boughman was -- I wanted to crystallize a point that she made and up until she said that, I would have said I don't care about accuracy. This goes back to the issue we were talking about a few minutes ago, the components of the accuracy or the components of the inaccuracy, whether it is strips or whether it is use or stuff like that, as long as we have a final number.

But you suggested -- what you said made me realize that, in fact, if we knew where the differences were, then by labeling, we may have a great educational impact. For example, if it turns out that the majority of an error -- of the error for a certain machine or a certain system were in the strips, then that would be an important thing to point out in the sense that the consumer would then know how important it is to handle the strips. That is much more important than something else.

If a large part of the error were in preparation of the skin or something like that, some other component,

then that would give us a handle to -- the consumer a handle to improve the results on their own.

So, I think that leaves us to making -considering suggestions to modify how the original
manufacturer brings their data to us. I just wanted to
crystallize that point.

DR. NIPPER: I think that is really an important point.

Other members of the panel may have other questions or concerns for our speakers while they are here.

DR. CLEMENT: Just one brief comment on Ms.

Dillard's presentation. I thought it was very clever and very innovative to lump the patient as part of the testing device. I think that is a very important concept for the panel to keep in mind, as opposed to a laboratory device, where you -- it is very impersonal and it is just one little tube of blood and it is all based on the machine, the technology and clearly from my experience is that the patient is probably the most important part of the device to make it work and I am sure with the non-invasive technologies, even more so.

I was just reading over the guidance. Dr. Gutman does spend a lot of time talking about patient issues, user

error and so forth, but I think if that could be even more emphasized, that this really is a wholly different technology where the patient is actually part of the machine to actually get an outcome result, that is extremely important to remember.

DR. NIPPER: Those of us, Dr. Clement, who are old enough to remember when large numbers of laboratory tests for a manual will remember with nostalgia when we considered the technologist part of the device and we were instructed by our mentors to -- when you are determining what coefficient of variation is achievable on a test, you put your best tact on it so that we give everybody else a chance, something to shoot at.

So, some of us are quite familiar with the operator as part of the device.

Other questions or concerns? Yes, Dr. Zawadzki.

DR. ZAWADZKI: Ms. Rooks raised the issue of certain criteria that the FDA should follow. One of the issues that was raised was whether the FDA should encourage the use of a specific reference methodology. I don't know if this issue will be discussed further tomorrow, but it just occurs to me that a lot of the reference methodology is really not clear with the current meters, that some of us

know to what a given meter is referenced and the majority of people really don't know.

We spent a lot of time discussing a 20 percent variation in the Cox diagram, but you can have 15 percent variation just between a capillary and a plasma reading. So, I would just suggest that it would be very useful to know what specific methodology a given meter has and to have that clearly outlined in the inserts and currently I have not found that.

DR. NIPPER: I am also -- I have been sitting here thinking -- it doesn't have a thing to do with it being the cocktail hour, but I was thinking of the analogy between the capillary blood glucose meters versus serum analyzers and the measurement of blood versus breath alcohol. There are many similarities in this issue and there are, obviously, some very important differences. But, you see, we are talking about the measurement technique or several measurement techniques that are designed to get at one particular piece of information.

The translation of a breath alcohol concentration into an apparent blood alcohol concentration is packed with assumptions that we tend to gloss over, but there are still some assumptions and I know this issue is very complex -- is

made much more complex by the fact that we have whole blood from venous sources, whole blood from -- plasma or serum from venous sources and then capillary whole blood to deal with that makes the quality control issues, the calibration issues extremely complex.

I am wondering if we shouldn't maybe try not -maybe we should try to translate those into the same number.
Maybe we should try to say they are totally different
numbers, that we are measuring totally different things and
that the meaning is totally different. I would like us -- I
would like one of the things that we take home to think
about tonight for tomorrow's deliberations, about whether we
want the capillary blood glucose meter to read in serum
venous units or whether we really care whether they
correlate or not.

In other words, are we asking too much or not enough? I think there have been a number of issues raised today. One of them is that, of course, that these apparently simple devices have very different uses across the spectrum from lay use in determining dosage and compliance with diet regimens and insulin administration, all the way toward treatment of acutely ill patients, who are not diabetic at the bedside in hospitals.

I am also wondering if that doesn't complicate the equation to such an extent that it may be ballooned into an insolvable problem. So, I would like us to think about -- I don't want to make this Ms. Rooks' definition, but she is the one who put it on the board, that portable blood glucoses devices are intended for use. I would like us to think about what that blank -- what is in that blank and to decide if we can make this problem manageable if we change that definition or if we ask the FDA to consider other areas.

We are approaching the 5:30 hour. I am not sure whether we can do Meeting Goal No. 2 today. I am kind of glucosed out, to be honest with you. And I would like us to take our goal documents and the things that we have heard today, especially those from the patients who have made an impassioned and valid plea for us to try to help the particular situation that they have and come back refreshed tomorrow to hear other issues and deal with these particular goals.

I would like us to remember that tomorrow we have some dealings with quality systems regulations, with human factors and that we have more speakers who will address issues about these topics and we will have some breaks for

open committee sessions when we can deal with Goals 2 through 5.

We will try to get finished at a reasonable hour tomorrow, but I would like us to do as much as we can to help Dr. Gutman and his staff deal with these particular issues. I think this has been one of the most challenging topics that we have -- in my experience on the panel to deal with and, yet, it is one that I think the panel can have a wide-reaching impact on.

Does anyone have anything else to add before I adjourn the panel for today?

DR. BOUGHMAN: I do have a quick question.

For those of us who have confidential material that could be left behind or could be disposed of, is there a place we can put those?

MS. LAPPALAINEN: Yes. You need to leave your documents on the table and we will destroy them and account for them. We do account for them.

The panel packages, which have -- regarding the meeting and not the particular device you need to keep and take that.

DR. BOUGHMAN: Okay. Thank you.

MS. LAPPALAINEN: Just leave the documents at your

place.

DR. BOUGHMAN: Thank you.

DR. NIPPER: Anything you leave at your place will be shredded, except for the peppermints.

Yes, there is one other issue.

DR. RICHTER: Before we adjourn -- my name is

Kimberly Richter. I am the deputy director in the Office of

Device Evaluation at FDA.

I think there is one question we have to wrap up this part of the discussion that I would at least appreciate a brief thought on and that is we have presented you with the MDR information, the adverse events, not only to give you a sense of what types of complaints we get, but also an overall sense of the number that we get in the context of the millions of uses that we have each year.

Tomorrow morning we are going to be off talking about quality systems and other kinds of specific controls and things that relate to the guidance document. But I think that we would also like some sense from the panel as to whether this level of adverse events even is significant with the number and the wide range of uses that these products have.

If you are talking about -- I think the number was

approximately 800 complaints a year and you are talking about three million users who are using these products daily, in that context I know you will be thinking about that with your more specific discussions tomorrow. But if anyone has a comment on that now, if it is all right with the chairman, I would appreciate --

DR. NIPPER: The chairman would like you to define what "significant" means to you.

DR. RICHTER: I think we are looking for the panel to give us an indication. I mean, we are looking at should we be modifying our guidance and should we be taking any other actions? Should we be concerned that these products are not appropriately safe and effective, as we have been regulating them? I think that that is the question.

And is there something else we should be looking at? Before we get off into what specific things we can do to improve our guidance, I think we would like to know do you think that there is a problem here. I think it is a very general basic first step question.

Does this number of MDRs raise a concern?
DR. NIPPER: Dr. Rosenbloom.

DR. ROSENBLOOM: Well, that gets back to the question of what kind of problems are these and we asked

that question before and the data is not readily available. So, I don't think we are in a position to respond to the significance question without knowing the significance of the adverse events.

DR. NIPPER: If you look at the -- the answer to your question, I think, is in the handout. One of the those really neat bar graphs talked about the kinds of adverse events. Thirty-two percent of these numbers, of the adverse event reports, were characterized involving for the most part hospitalization and emergency treatment.

So, I would consider -- my personal opinion is that if someone is having a significant number of hospitalizations, emergency treatments and there were a couple of deaths down there, my guess is they are significant adverse events.

DR. ROSENBLOOM: So, that is a definition of serious adverse events, involves death, development of cancer, hospitalization. There are four or five criteria.

DR. NIPPER: Right.

DR. ROSENBLOOM: I guess the question then is could we do a sampling of these and determine if the -- these are adverse events which are different than side

effects or adverse effects of the use of the blood glucose meter. So, we do not know -- we still don't know whether the errors associated with or determined to be associated with the use of the blood glucose monitoring device were causal.

DR. NIPPER: Right. All we know is that the strip is most often named.

DR. ROSENBLOOM: I know of a case that I am involved with medically legally, where the home use of the device, for whatever reason, it was badly supervised for years, was reading normal or low blood glucoses and the person came in with a very high blood glucose and died. But, you know, that could be -- the problem was not the meter. The problem was otherwise.

DR. NIPPER: And the point that Dr. Boughman --

DR. ROSENBLOOM: But it was associated --

DR. NIPPER: -- was that the patient is part of the system. Okay? So, we may need to do things that will enhance the efficacy of that system.

DR. BOUGHMAN: I would answer your question in two or three different ways, focusing in on the word "significant." If there is even one adverse event that really is caused or has a causal portion to it, then that is

important. Nonetheless, as a genetic epidemiologist, I am consistently impressed by the denominators that we have here; the numbers of patients, the numbers of tests that really do constitute the denominator.

I think we need to balance those when you are talking about a surveillance system so that although every event or adverse event is extremely important, on the other hand, given the complexity of the situation, I am fairly favorably impressed by the ratio of adverse events in a system that is often used by lay people or at least a large proportion of them, under fairly loose circumstances in certain situations and I think it does bring us back to one more issue in the examination where things started out being put in the user category, but then shifted over and were shown to be in the device category.

That made me sit up and take notice, reminding me of a panel's obligation and a manufacturer's obligation to, in fact, present and review as complete a data set as we can at the outset, so that, in fact, we by the time the manufacturer comes for a 510(k) review, then, in fact, many of the glitches that would have been related to the device, in fact, have been worked through.

But that is an obligation that I feel very

strongly about and reminds us that we have to be careful in that initial process.

DR. NIPPER: Yes. Dr. Harrington Falls.

DR. HARRINGTON FALLS: I just had a comment.

First, the hundreds of millions of tests that are done and then these relative 7,000 reports; secondly, the patients are inherently ill to begin with. So, it might be an association, not a cause and effect. And then, thirdly, I am more interested in finding out which of these monitors are the optimal ones, which are the ones we should be recommending that have better technology and are still cost effective for the patient.

DR. ROSENBLOOM: That is another datum we should have is whether these reports are associated with particular instruments or evenly distributed across the spectrum.

DR. NIPPER: Dr. Clement.

DR. CLEMENT: I would echo Dr. Rosenbloom's comment. That was my identical thought is that we are basically looking for -- we are trending data and trying to get a sort of global feeling. But that would be one trending of the data that would be extremely important to be able to determine --

MS. DILLARD: Let me caution you because the -- as

I tried to point out with the limitations of our systems and, again, it is worth another couple of days worth of discussion -- you can't use this data that way because of the variability in reporting patterns, the logical gyrations that people go through to try not to report and still meet their reporting obligations under the mandatory system. And the challenge, I think, Dr. Richter laid upon you is we have this information. We know what is reported to us. You deal with patients on a daily basis. You deal with results from these systems on a daily basis. You know what is going on. Think about what you report to us. Think about what your clinical experience is and what that means and what kind of information we have from you in our system that you may be aware of.

And I think the challenge for you is to help us understand what the data we have really means when you translate that into, quote, the real world.

DR. NIPPER: Dr. Habig, you had a comment?

DR. HABIG: Yes, I do. It seems clear that while there is an FDA database on MDR reporting and it has been analyzed in some careful ways, it is -- I have a personal opinion here -- not interpretable. There is a lot of information there and you can make bar graphs and show

percentages and things, but I am concerned that the panel might come away thinking there is a serious problem.

Several recent commenters on the panel, I think, would agree with me that there is not a serious problem if serious problem is looked at by events per measurement or events per millions of strips and meters used.

It is a small total number of reported -- and I will try to use the term correctly -- of alleged reported adverse events. As manufacturers, most manufacturers with 800 number complaint systems is where most of this information comes from, record every complaint. It is a requirement of quality system regulations, good manufacturing practice. They are investigated and inspected by FDA investigators on those specific issues.

My experience with one manufacturer where I used to work is that the procedures for determining whether this should be reported are very conservative. If it is alleged, it is reported. We sometimes -- they, now, sometimes follow up and determine that, yes, it was a user error; it was an outdated strip; it was a dirty meter, whatever. I think that in general the reporting from manufacturers, based on those 800 number complaint systems is very zealously done.

Even with that, the number of reported events per

thousand, ten thousand, hundred thousand uses is really low. I am not going to remember the number exactly but when Dr. Sullivan was the Secretary and was in a hearing, he reported a number like .00043 percent. It is a very small number.

Back to my personal opinion, my personal opinion is the data does not show a problem. It might not not show a problem. It is simply not interpretable. And I want to be sure that we don't determine that there is a problem to address without actually knowing that there is a problem.

DR. NIPPER: Your comment is well taken, Bob. I have been sitting here thinking about some history that Dr. Aziz(?) probably would prefer to forget, that dealt with glucose a number of years ago on a clinical laboratory device, where it was possible for the technologist to look at substrate exhaustion before reporting out a low number, look for substrate exhaustion, probably did not check it closely or was not flagged to check for it closely, reported a low number. It was high. And a patient had an adverse effect.

That caused a significant change in the way that manufacturers handle or handled that particular problem.

What I think we -- I think you and I are on the same wave length. If we can get a handle on a problem, no matter how

small, we would like to let the FDA know about it so that we can help manufacturers and, therefore, help the public fix the problem.

I am not sure we have a handle on the problem. We have kicked it around a good bit today. I don't know whether -- I can't find a handle yet. So, I would like to ask the panel, to second Bob's point, that we need to look for a handle. Let's see if we have a problem. If we find the problem, let's deal with it. If we can't find the problem, no matter how hard we would like to, no matter how much we suspect there may be one, let's encourage the FDA to try to get a better handle on this issue if it can.

Somebody else had a hand up over here first.

Ms. Rosenthal.

MS. ROSENTHAL: It just occurred to me that if we don't have a handle on it -- and I do agree that we don't -- and it is a small number, might it be advisable to step back and start recollecting data in a way that is more interpretable?

DR. NIPPER: That was the blank I was leaving open for us to think about tonight. Yes. Because I don't know whether we have got enough data. I don't know whether we need -- I would like us to think about what we saw. This

data is worth looking at again. It is worth thinking about carefully before we jump into something.

On the other hand, I don't want us to be remiss as a panel and miss an opportunity to deal with a problem that could affect, as someone so eloquently put it, a single life.

Dr. Rosenbloom.

DR. ROSENBLOOM: Yes. Again, I think that we may be dealing with the tip of an iceberg with this data, but if it is the tip of an iceberg, it should give us some information. I think that looking at the most serious adverse events in this database, we may find situations like the one I am familiar with, where there was a total lack of following manufacturer's recommendations and medical supervision and the device was just not functioning properly, but it wasn't serviced properly. It wasn't being taken care of properly.

So, if we find that the serious adverse events that result in ketoacidosis, that result in death, if we sample 20 or 30 of those and find that they are all associated with either inadequate emphasis on certain maintenance requirements, then we should make a very strong recommendation for that to be included in the system.

DR. NIPPER: And that may be an labeling issue --

DR. ROSENBLOOM: A labeling issue or even a registration issue. I mean, we may want to make a recommendation that everyone who buys one of these is sent a postcard every four months that they have to get their machine in and get it serviced. I mean, you know, that is not a recommendation, but, you know, that is conceivably the kind of thing that could come out of finding that five people have died because they have machines that -- in 1995, because their care giver -- five children have died because their care giver bought a machine and didn't do a darn thing with it for three years, never brought it to the clinic or never got any supervision, that sort of thing.

You know, we may have no way of dealing with it or we may have recommendations. But I think we ought to look closely at the data.

DR. NIPPER: I am assuming you are speaking hypothetically about five children dying.

DR. ROSENBLOOM: Oh, yes, yes, yes.

DR. NIPPER: Just to make sure that we all don't take that away as --

DR. ROSENBLOOM: I don't even know what the number -- that percentage reflected, the deaths. What was the n

there? And we have no idea what the age group is.

MS. DILLARD: Historically, the total number of death reports that we have received in association with these devices -- and I want to make it clear that it is an allegation and there is no cause and effect -- is 55 in total.

DR. ROSENBLOOM: That is a lot. That is enough data to look at.

DR. NIPPER: Are there any other comments? Did we answer your question?

DR. RICHTER: Thank you very much.

DR. NIPPER: You are welcome.

Unless I hear an objection to the contrary, the panel is adjourned until tomorrow morning at 8 o'clock.

[Whereupon, at 5:38 p.m., the meeting was recessed, to reconvene at 8:00 a.m., the following morning, Friday, March 21, 1997.]